

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,  
LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULAIN  
L2 110146 S CALMODULIN  
L3 342878 S SERINE OR THREONINE  
L4 73725 S L3 AND KINASE  
L5 6021 S L2 AND L4  
L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
L7 391 S L5 AND L6  
L8 195 S HUMAN AND L7  
L9 1023024 S DOMAIN?  
L10 111 S L7 AND L9  
L11 345 S DAP(A) KINASE?  
L12 72 S L10 AND L11  
L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W) END OR C-TERMINAL  
L15 34 S L10 AND L14  
L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
L17 10019 S "DAP"  
L18 6 S L16 AND L17  
L19 4269 S "ZIP"  
L20 2 S L16 AND L19  
L21 98 S "DRP-1"  
L22 1 S L16 AND L21  
E KIMCHI A/AU  
L23 484 S E3  
L24 3 S L16 AND L23  
L25 3 DUP REM L24 (0 DUPLICATES REMOVED)  
L26 1 S L25 AND DRP##  
L27 7 S L23 AND DRP##  
L28 2 DUP REM L27 (5 DUPLICATES REMOVED)  
L29 81 S L23 AND L17  
L30 18 S L29 AND L14  
L31 6 DUP REM L30 (12 DUPLICATES REMOVED)  
L32 15 S L16 AND REGULAT?  
L33 15 DUP REM L32 (0 DUPLICATES REMOVED)  
L34 3919 S "DEATH DOMAIN?"  
L35 19 S L15 AND L34  
L36 5 DUP REM L35 (14 DUPLICATES REMOVED)  
L37 43518 S "DOMINANT NEGATIVE"  
L38 5 S L16 AND L37

=>

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NEWS 4 Feb 01 DKILIT now produced by FIZ Karlsruhe and has a new update frequency  
NEWS 5 Feb 19 Access via Tymnet and SprintNet Eliminated Effective 3/31/02  
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NEWS 7 Mar 22 TOXLIT no longer available  
NEWS 8 Mar 22 TRCTHERMO no longer available  
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NEWS 18 Apr 22 Federal Research in Progress (FEDRIP) now available  
NEWS 19 May 31 PCTFULL to be reloaded. File temporarily unavailable.  
NEWS 20 Jun 03 New e-mail delivery for search results now available  
  
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CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),  
AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002  
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```
=> s calmodulain
L1          0 CALMODULAIN

=> s calmodulin
L2         110146 CALMODULIN

=> s serine or threonine
L3         342878 SERINE OR THREONINE

=> s l3 and kinase
L4         73725 L3 AND KINASE

=> s l2 and l4
L5         6021 L2 AND L4

=> s (cell (a) death) or apoptosis
    3 FILES SEARCHED...
L6         422053 (CELL (A) DEATH) OR APOPTOSIS

=> s l5 and l6
L7         391 L5 AND L6

=> s human and l7
L8         195 HUMAN AND L7

=> s domain?
L9         1023024 DOMAIN?

=> s l7 and l9
L10        111 L7 AND L9

=> s DAP(a)kinase?
L11        345 DAP(A) KINASE?

=> s l10 and l11
L12        72 L10 AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13        23 DUP REM L12 (49 DUPLICATES REMOVED)
```

=> d 1-23 ibib ab

L13 ANSWER 1 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)  
ACCESSION NUMBER: 2002:89428 SCISEARCH  
THE GENUINE ARTICLE: 513UP  
TITLE: **DAP kinase** activity is critical for  
C-2-ceramide-induced **apoptosis** in PC12 cells  
AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S;  
Uchino S  
CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,  
Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,  
Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi  
Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut  
Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan  
COUNTRY OF AUTHOR: Japan  
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.  
1, pp. 139-147.  
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD,  
OXFORD OX2 ONE, OXON, ENGLAND.  
ISSN: 0014-2956.  
DOCUMENT TYPE: Article; Journal  
LANGUAGE: English  
REFERENCE COUNT: 41

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent  
**apoptosis**. Here, we investigate the involvement of  
death-associated protein (**DAP kinase**), initially  
identified as a positive mediator of the interferon-gamma-induced  
**apoptosis** of HeLa cells, in the C-2-ceramide-induced  
**apoptosis** of PC 12 cells. **DAP kinase** is  
endogenously expressed in these cells. On exposure of PC 12 cells to 30  
muM C-2-ceramide, both the total (assayed in the presence of Ca2+/  
**calmodulin**) and Ca2+/**calmodulin**-independent (assayed in  
the presence of EGTA) **DAP kinase** activities were  
transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and  
then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30  
muM C-2-ceramide, the Ca2+/**calmodulin** independent activity/total  
activity ratio increased from 0.22 to 0.60. These effects were dependent  
on the C-2-ceramide concentration. C-8-ceramide, another active ceramide  
analog, also induced **apoptosis** and activated **DAP**  
**kinase**, while C-2-dihydroceramide, an inactive ceramide analog,  
failed to induce **apoptosis** and increase **DAP**  
**kinase** activity. Furthermore, transfection studies revealed that  
overexpression of wild-type **DAP kinase** enhanced the  
sensitivity to C-2- and C-8-ceramide, while a catalytically inactive  
**DAP kinase** mutant and a construct containing the death  
**domain** and C-terminal tail of **DAP kinase**,  
which act in a dominant-negative manner, rescued cells from C-2-, and  
C-8-ceramide-induced **apoptosis**. These findings demonstrate that  
**DAP kinase** is an important component of the apoptotic  
machinery involved in ceramide-induced **apoptosis**, and that the  
intrinsic **DAP kinase** activity is critical for  
ceramide-induced **apoptosis**.

L13 ANSWER 2 OF 23 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2001691904 MEDLINE  
DOCUMENT NUMBER: 21601623 PubMed ID: 11579085  
TITLE: The pro-apoptotic function of death-associated protein  
**kinase** is controlled by a unique inhibitory  
autophosphorylation-based mechanism.  
AUTHOR: Shohat G; Spivak-Kroizman T; Cohen O; Bialik S; Shani G;

Berrisi H; Eisenstein M; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
 Science, Rehovot 76100, Israel.  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Dec 14) 276 (50)  
 47460-7.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200201  
 ENTRY DATE: Entered STN: 20011213  
 Last Updated on STN: 20020128  
 Entered Medline: 20020124

AB Death-associated protein **kinase** is a calcium/**calmodulin**  
**serine/threonine kinase**, which positively  
 mediates programmed **cell death** in a variety of  
 systems. Here we addressed its mode of regulation and identified a  
 mechanism that restrains its apoptotic function in growing cells and  
 enables its activation during **cell death**. It involves  
 autophosphorylation of Ser(308) within the **calmodulin**  
 (CaM)-regulatory **domain**, which occurs at basal state, in the  
 absence of Ca(2+)/CaM, and is inversely correlated with substrate  
 phosphorylation. This type of phosphorylation takes place in growing cells  
 and is strongly reduced upon their exposure to the apoptotic stimulus of  
 C(6)-ceramide. The substitution of Ser(308) to alanine, which mimics the  
 ceramide-induced dephosphorylation at this site, increases  
 Ca(2+)/CaM-independent substrate phosphorylation as well as binding and  
 overall sensitivity of the **kinase** to CaM. At the cellular level,  
 it strongly enhances the death-promoting activity of the **kinase**.  
 Conversely, mutation to aspartic acid reduces the binding of the protein  
 to CaM and abrogates almost completely the death-promoting function of the  
 protein. These results are consistent with a molecular model in which  
 phosphorylation on Ser(308) stabilizes a locked conformation of the  
 CaM-regulatory **domain** within the catalytic cleft and  
 simultaneously also interferes with CaM binding. We propose that this  
 unique mechanism of auto-inhibition evolved to impose a locking device,  
 which keeps death-associated protein **kinase** silent in healthy  
 cells and ensures its activation only in response to apoptotic signals.

L13 ANSWER 3 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)  
 ACCESSION NUMBER: 2001:869068 SCISEARCH  
 THE GENUINE ARTICLE: 485XR  
 TITLE: Identification of a new form of death-associated protein  
**kinase** that promotes cell survival  
 AUTHOR: Jin Y J; Blue E K; Dixon S; Hou L; Wysolmerski R B;  
 Gallagher P J (Reprint)  
 CORPORATE SOURCE: Indiana Univ, Sch Med, Dept Cellular & Integrated Physiol,  
 635 Barnhill Dr, Indianapolis, IN 46202 USA (Reprint);  
 Indiana Univ, Sch Med, Dept Cellular & Integrated Physiol,  
 Indianapolis, IN 46202 USA; St Louis Univ, Sch Med, Dept  
 Pathol, St Louis, MO 63104 USA  
 COUNTRY OF AUTHOR: USA  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (26 OCT 2001) Vol. 276,  
 No. 43, pp. 39667-39678.  
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC,  
 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.  
 ISSN: 0021-9258.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 43  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB In this study, two alternatively spliced forms of the mouse death-associated protein **kinase** (DAPK) have been identified and their roles in **apoptosis** examined. The mouse DAPK-alpha sequence is 95% identical to the previously described human DAPK, and it has a **kinase domain** and **calmodulin-binding** region closely related to the 130-150 kDa myosin light chain **kinases**. A beta -residue extension of the carboxyl terminus of DAPK-beta distinguishes it from the human and mouse DAPK-alpha. DAPK phosphorylates at least one substrate in vitro and in vivo, the myosin II regulatory light chain. This phosphorylation occurs preferentially at Ser-19 and is stimulated by calcium and **calmodulin**. The mRNA encoding DAPK is widely distributed and detected in mouse embryos and most adult tissues, although the expression of the encoded 160-kDa DAPK protein is more restricted. Overexpression of DAPK-alpha, the mouse homolog of human DAPK has a negligible effect on tumor necrosis factor (TNF)-induced **apoptosis**. Overexpression of DAPK-beta has a strong cytoprotective effect on TNF-treated cells. Biochemical analysis of TNF-treated cell lines expressing mouse DAPK-beta suggests that the cytoprotective effect of DAPK is mediated through both intrinsic and extrinsic apoptotic signaling pathways and results in the inhibition of cytochrome c release from the mitochondria as well as inhibition of caspase-3 and caspase-9 activity. These results suggest that the mouse DAPK-beta is a negative regulator of TNF-induced **apoptosis**.

L13 ANSWER 4 OF 23 MEDLINE DUPLICATE 2  
 ACCESSION NUMBER: 2001236583 MEDLINE  
 DOCUMENT NUMBER: 21214579 PubMed ID: 11313923  
 TITLE: Promoter methylation of **DAP-kinase**:  
 association with advanced stage in non-small cell lung  
 cancer.  
 AUTHOR: Kim D H; Nelson H H; Wiencke J K; Christiani D C; Wain J C;  
 Mark E J; Kelsey K T  
 CORPORATE SOURCE: Department of Environmental Health, Harvard School of  
 Public Health, 665 Huntington Avenue, Boston,  
 Massachusetts, MA 02115, USA.  
 CONTRACT NUMBER: CA06717 (NCI)  
 CA08357 (NCI)  
 CA74386 (NCI)  
 ES/CA 06409 (NIEHS)  
 SOURCE: ONCOGENE, (2001 Mar 29) 20 (14) 1765-70.  
 Journal code: ONC; 8711562. ISSN: 0950-9232.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200105  
 ENTRY DATE: Entered STN: 20010517  
 Last Updated on STN: 20010517  
 Entered Medline: 20010503

AB Death associated protein (**DAP**)-**kinase** is a 16 kDa **calmodulin-dependent serine/threonine kinase** that carries a death **domain** at its C-terminus. **DAP-kinase** functions as a positive mediator of **apoptosis** that is induced by interferon-gamma. Recent studies suggest that **DAP-kinase** is involved in tumor metastasis and that it can be inactivated by methylation of CpG islands in the promoter region of the gene in some human tumors. However, little is known about the factors that are associated with the occurrence of **DAP-kinase** promoter methylation. We investigated both the possible associations of tobacco carcinogen and asbestos exposure with **DAP-kinase** promoter methylation, and the demographic and clinical factors associated with **DAP-kinase** promoter

methylation in non-small cell lung cancer (NSCLC). One hundred and eighty-five patients diagnosed with NSCLC undergoing surgical resection from June, 1992 through December, 1996 at Massachusetts General Hospital participated in this study. Methylation-Specific PCR (MSP), performed using fresh-frozen tissue, was used to determine the methylation status of the promoter region of the **DAP-kinase** gene.

Forty-seven (25%) of 185 tumors showed **DAP-kinase** promoter methylation. There was a significant association between methylation and an advanced pathologic stage ( $P=0.003$ , Fisher's exact test). Methylation of the **DAP-kinase** promoter was also associated with an increase in tumor size ( $P=0.009$ , Fisher's exact test) and lymph node involvement ( $P=0.04$ ). No association was found between promoter methylation of **DAP-kinase** and k-ras or p53 mutation. In addition there was no association with a history of exposure to tobacco or asbestos. Controlling for age, sex, and histology, the odds ratios describing the association of **DAP-kinase** hypermethylation with stage were 2.70 (1.13--6.45), 3.11 (1.37--7.08) and 7.77 (1.21--50.03) in stages II, III and IV, respectively. Stage I cases with **DAP-kinase** promoter methylation had worse overall survival, but with the small sample size and limited follow-up this did not reach statistical significance. Our findings suggest that methylation of the promoter region of the **DAP-kinase** gene is not associated with exposure to tobacco or asbestos. However, they strongly suggest that **DAP-kinase** may be important in the progression of non-small cell lung cancer from early to late stage disease.

L13 ANSWER 5 OF 23 MEDLINE  
ACCESSION NUMBER: 2002071410 MEDLINE  
DOCUMENT NUMBER: 21656623 PubMed ID: 11797395  
TITLE: Hypermethylation of **DAP-kinase** gene CpG  
Island in malignant lymphoma with B-cell phenotype.  
AUTHOR: Nakatsuka S; Takakuwa T; Aozasa K  
CORPORATE SOURCE: Department of Pathology, Osaka University Graduate School  
of Medicine, Suita 565-0871.  
SOURCE: RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (2001  
Dec) 49 (12) 1242-7. Ref: 17  
Journal code: 2984781R. ISSN: 0047-1860.  
PUB. COUNTRY: Japan  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200203  
ENTRY DATE: Entered STN: 20020125  
Last Updated on STN: 20020311  
Entered Medline: 20020308

AB Death-associated protein-kinase (**DAP-Kinase**)  
is a pro-apoptotic **serine/threonine kinase**  
with a death **domain**, which is involved in **apoptosis**  
induced by interferon-gamma, tumor necrosis factor-alpha, and Fas ligand.  
Epigenetic down-regulation of **DAP-Kinase** gene  
expression by hypermethylation of its promoter region was reported in  
certain kinds of malignancies. Previous patho-epidemiological studies  
indicated that thyroid lymphoma (TL) evolves among active lymphoid cells in  
chronic lymphocytic thyroiditis (CLTH). With the use of methylation  
specific polymerase chain reaction, methylation status of **DAP-**  
**Kinase** CpG island was examined in thyroid lesions of 19 cases with  
TL and 9 with CLTH. Frequency of methylation was higher in TL cases (16 of  
19, 84.2%) than in CLTH cases (2 of 9, 22.2%) ( $p < 0.01$ ). DNA extracted  
from peripheral blood leukocytes from TL and CLTH cases never showed

methylation, indicating that the methylation occurred somatically in lesional lymphocytes in the thyroid. We also examined the methylation status of **DAP-kinase** gene in 16 cases of T-cell malignancies including eight adult T-cell leukemia/lymphoma and 24 NK/T-cell, 34 B-cell, and two immunophenotypically undetermined lymphomas. Frequency of methylation was higher in B-cell (27 of 34, 79.4%) than in T-cell malignancies (eight of 16, 50%) ( $p < 0.05$ ). Fifteen of 24 (62.5%) NK/T-cell lymphomas showed DNA methylation. Hematopoietic cell lines with a methylated gene were resistant to **apoptosis**. Treatment of the cells with a demethylating agent restored apoptotic **cell death** in one B-cell lymphoma cell line with DNA methylation. Our results suggested that suppression of **DAP-Kinase** expression by DNA methylation might play a role in the development of B-cell malignancies.

L13 ANSWER 6 OF 23 MEDLINE DUPLICATE 3  
 ACCESSION NUMBER: 2001216755 MEDLINE  
 DOCUMENT NUMBER: 21153208 PubMed ID: 11230133  
 TITLE: Autophosphorylation restrains the apoptotic activity of DRP-1 **kinase** by controlling dimerization and **calmodulin** binding.  
 AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.  
 Journal code: 8208664. ISSN: 0261-4189.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200104  
 ENTRY DATE: Entered STN: 20010425  
 Last Updated on STN: 20020420  
 Entered Medline: 20010419

AB DRP-1 is a pro-apoptotic Ca<sup>2+</sup>/**calmodulin** (CaM)-regulated **serine/threonine kinase**, recently isolated as a novel member of the **DAP-kinase** family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory **domain**. A negative charge at this site reduces both the binding to CaM and the formation of DRP-1 homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor- $\alpha$  death receptors, increases the formation of DRP-1 dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory **domain** and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of DRP-1, and a target for efficient activation of the **kinase** by various apoptotic stimuli.

L13 ANSWER 7 OF 23 MEDLINE  
 ACCESSION NUMBER: 2001537809 MEDLINE  
 DOCUMENT NUMBER: 21457157 PubMed ID: 11573098  
 TITLE: Crystal structures of the catalytic **domain** of human protein **kinase** associated with **apoptosis** and tumor suppression.  
 COMMENT: Comment in: Nat Struct Biol. 2001 Oct;8(10):824-6



AUTHOR: Tereshko V; Teplova M; Brunzelle J; Watterson D M; Egli M  
CORPORATE SOURCE: Department of Biological Sciences, Vanderbilt University,  
Nashville, Tennessee 37235, USA.  
SOURCE: NATURE STRUCTURAL BIOLOGY, (2001 Oct) 8 (10) 899-907.  
Journal code: B98; 9421566. ISSN: 1072-8368.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: PDB-1IG1; PDB-1JKK; PDB-1JKL; PDB-1JKS; PDB-1JKT  
ENTRY MONTH: 200110  
ENTRY DATE: Entered STN: 20011008  
Last Updated on STN: 20011022  
Entered Medline: 20011018

AB We have determined X-ray crystal structures with up to 1.5 Å resolution of the catalytic **domain** of death-associated protein **kinase** (DAPK), the first described member of a novel family of pro-apoptotic and tumor-suppressive **serine/threonine kinases**. The geometry of the active site was studied in the apo form, in a complex with nonhydrolyzable AMPPnP and in a ternary complex consisting of **kinase**, AMPPnP and either Mg<sup>2+</sup> or Mn<sup>2+</sup>. The structures revealed a previously undescribed water-mediated stabilization of the interaction between the lysine that is conserved in protein **kinases** and the beta- and gamma-phosphates of ATP, as well as conformational changes at the active site upon ion binding. Comparison between these structures and nucleotide triphosphate complexes of several other **kinases** disclosed a number of unique features of the DAPK catalytic **domain**, among which is a highly ordered basic loop in the N-terminal **domain** that may participate in enzyme regulation.

L13 ANSWER 8 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001349009 EMBASE  
TITLE: A **cell death**-promoting **kinase**

AUTHOR: Kimchi A.  
CORPORATE SOURCE: A. Kimchi, Department of Molecular Genetics, Weizmann  
Institute of Science, Rehovot 76100, Israel.  
adi.kimchi@weizmann.ac.il  
SOURCE: Nature Structural Biology, (2001) 8/10 (824-826).  
Refs: 22  
ISSN: 1072-8368 CODEN: NSBIEW  
COUNTRY: United States  
DOCUMENT TYPE: Journal; (Short Survey)  
FILE SEGMENT: 016 Cancer  
029 Clinical Biochemistry  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Death-associated protein **kinase** (DAP-**kinase**; DAPk) has been implicated in programmed **cell death** and tumor suppression. The recently solved crystal structure of the catalytic **domain** of human DAP-**kinase** reveals interesting 'fingerprint' regions that may be functionally important.

L13 ANSWER 9 OF 23 MEDLINE

ACCESSION NUMBER: 2001169641 MEDLINE  
DOCUMENT NUMBER: 21167344 PubMed ID: 11268041  
TITLE: The DAP **kinase** family of pro-apoptotic proteins: novel players in the apoptotic game.  
AUTHOR: Kogel D; Prehn J H; Scheidtman K H  
CORPORATE SOURCE: Interdisciplinary Center for Clinical Research (IZKF),  
University of Munster, Germany.. koegel@uni-muenster.de  
SOURCE: BIOESSAYS, (2001 Apr) 23 (4) 352-8. Ref: 47

Journal code: 9YY; 8510851. ISSN: 0265-9247.  
PUB. COUNTRY: England: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010604  
Last Updated on STN: 20010604  
Entered Medline: 20010531

AB The DAP (Death Associated Protein) **kinase** family is a novel subfamily of pro-apoptotic **serine/threonine kinases**. All five **DAP kinase** family members identified to date are ubiquitously expressed in various tissues and are capable of inducing **apoptosis**. The sequence homology of the five **kinases** is largely restricted to the N-terminal **kinase domain**. In contrast, the adjacent C-terminal regions are very diverse and link individual family members to specific signal transduction pathways. There is increasing evidence that **DAP kinase** family members are involved in both extrinsic and intrinsic pathways of **apoptosis** and may play a role in tumor progression. This review will focus on structural composition and subcellular localization of **DAP kinase** family members and on signal transduction pathways leading to their activation. Potential mechanisms of **DAP kinase** family-mediated **apoptosis** will be discussed. BioEssays 23:352-358, 2001. Copyright 2001 John Wiley & Sons, Inc.

L13 ANSWER 10 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2001:624438 SCISEARCH

THE GENUINE ARTICLE: 459MQ

TITLE: A **serine/threonine kinase** which causes **apoptosis**-like cell **death** interacts with a calcineurin B-like protein capable of binding Na<sup>+</sup>/H<sup>+</sup> exchanger

AUTHOR: Matsumoto M; Miyake Y; Nagita M; Inoue H; Shitakubo D; Takemoto K; Ohtsuka C; Murakami H; Nakamura N; Kanazawa H (Reprint)

CORPORATE SOURCE: Osaka Univ, Grad Sch Sci, Dept Biol Sci, Machikaneyama Cho 1-16, Osaka 5600043, Japan (Reprint); Osaka Univ, Grad Sch Sci, Dept Biol Sci, Osaka 5600043, Japan; Okayama Univ, Fac Engn, Dept Biotechnol, Okayama, Japan

COUNTRY OF AUTHOR: Japan

SOURCE: JOURNAL OF BIOCHEMISTRY, (AUG 2001) Vol. 130, No. 2, pp. 217-225.

Publisher: JAPANESE BIOCHEMICAL SOC, ISHIKAWA BLDG-3F, 25-16 HONGO-5-CHOME, BUNKYO-KU, TOKYO, 113, JAPAN.  
ISSN: 0021-924X.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 45

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB We surveyed proteins capable of binding to the cytoplasmic **domain** of Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE)1 in a rat brain cDNA library with the yeast two-hybrid system. One clone obtained coded for a protein reported previously as a human calcineurin homologous protein (CHP). Since CHP is homologous to the regulatory subunit B of calcineurin, we expected a possible interacting partner of CHP like the catalytic subunit of calcineurin (calcineurin A), and surveyed this putative partner again with the yeast two-hybrid system. A clone thus obtained coded for a **kinase**, which is basically the same as that reported for human DRAK2. Overexpression of the rat homologue of DRAK2 caused

**apoptosis**-like cell death of NIH3T3 cells, which was dependent on the **kinase** activity, confirming the previous result for DRAK2. The purified CHP and rat DRAK2 proteins synthesized in *Escherichia coli* could bind in vitro. CHP and rat DRAK2 expressed in COS-7 cells were found to be localized in the Golgi apparatus and nucleus, respectively. Some of them was also found in the membrane peripheral region. When they were coexpressed in the same cells, most of CHP moved to the nucleus where rat DRAK2 is located, suggesting in vivo interaction of these proteins. However, minor but significant fractions of both proteins were also found in the membrane peripheral region. Rat DRAK2 is expressed highly in thymus, spleen, and testis, where the **apoptosis** plays an important role in physiology.

L13 ANSWER 11 OF 23 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2001434353 MEDLINE

DOCUMENT NUMBER: 21214809 PubMed ID: 11313698

TITLE: **DAP-kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.

AUTHOR: Cohen O; Kimchi A

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.

SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
Ref: 39  
Journal code: C7U; 9437445. ISSN: 1350-9047.

PUB. COUNTRY: England: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108

ENTRY DATE: Entered STN: 20010806  
Last Updated on STN: 20010806  
Entered Medline: 20010802

AB **DAP-kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of **DAP-kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich C-terminal tail, spanning the last 17 amino acids of the protein. A link between **DAP-kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of **DAP-kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of **DAP-kinase** was also studied experimentally in mouse model systems where the re-introduction of **DAP-kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP-**

**kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with **DAP-kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L13 ANSWER 12 OF 23 MEDLINE  
ACCESSION NUMBER: 2001042818 MEDLINE  
DOCUMENT NUMBER: 20541072 PubMed ID: 11092525  
TITLE: Role of hypermethylation of **DAP-kinase**  
CpG island in the development of thyroid lymphoma.  
AUTHOR: Nakatsuka S; Takakuwa T; Tomita Y; Miwa H; Matsuzuka F;  
Aozasa K  
CORPORATE SOURCE: Department of Patholog, Osaka University Graduate School of  
Medicine, Japan.  
SOURCE: LABORATORY INVESTIGATION, (2000 Nov) 80 (11) 1651-5.  
Journal code: KZ4. ISSN: 0023-6837.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200012  
ENTRY DATE: Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20001207

AB Death-associated protein-**kinase** (**DAP-Kinase**) is a **serine/threonine kinase** with a death **domain** that is involved in **apoptosis** induced by interferon-gamma, TNF-alpha, and Fas ligand. Epigenetic down-regulation of **DAP-Kinase** gene expression by hypermethylation of its promoter region was reported in B-cell malignancies. Previous pathoepidemiologic studies indicated that thyroid lymphoma (TL) evolves among active lymphoid cells in chronic lymphocytic thyroiditis (CLTH). With use of methylation-specific polymerase chain reaction, the methylation status of **DAP-Kinase** CpG island was examined in thyroid lesions of 19 cases with TL and 9 with CLTH. The frequency of methylation was higher in TL cases (16 of 19, 84.2%) than in CLTH cases (2 of 9, 22.2%) ( $p < 0.01$ ). DNA extracted from peripheral blood leukocytes from TL and CLTH cases never showed methylation, indicating that the methylation occurred somatically in the lesional lymphocytes in thyroid. These findings suggested that methylation of the **DAP-Kinase** promoter region might be involved in the development of TL from CLTH.

L13 ANSWER 13 OF 23 MEDLINE DUPLICATE 5  
ACCESSION NUMBER: 2000144081 MEDLINE  
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
TITLE: A functional genetic screen identifies regions at the C-terminal tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.  
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.  
Journal code: PV3; 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003  
ENTRY DATE: Entered STN: 20000330  
Last Updated on STN: 20000330  
Entered Medline: 20000323

AB Death-associated protein **kinase** (**DAP-kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP-kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP-kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP-kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the C-terminal tail of **DAP-kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the C-terminal **serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP-kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the C-terminal tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP-kinase** apoptotic function that does not affect the catalytic activity.

L13 ANSWER 14 OF 23 MEDLINE DUPLICATE 6  
ACCESSION NUMBER: 2000094983 MEDLINE  
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.  
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200002  
ENTRY DATE: Entered STN: 20000229  
Last Updated on STN: 20020420  
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to **DAP kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from **DAP kinase** and

displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, **DAP kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of **DAP kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by **DAP kinase**. Possible functional connections between **DAP kinase** and DRP-1 are discussed.

L13 ANSWER 15 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)  
 ACCESSION NUMBER: 1999:472355 SCISEARCH  
 THE GENUINE ARTICLE: 205ZF  
 TITLE: Death-associated protein **kinase** 2 is a new calcium/**calmodulin**-dependent protein **kinase** that signals **apoptosis** through its catalytic activity  
 AUTHOR: Kawai T; Nomura F; Hoshino K; Copeland N G; Gilbert D J; Jenkins N A; Akira S (Reprint)  
 CORPORATE SOURCE: HYOGO MED UNIV, DEPT BIOCHEM, 1-1 MUKOGAWA CHO, NISHINOMIYA, HYOGO 6638501, JAPAN (Reprint); HYOGO MED UNIV, DEPT BIOCHEM, NISHINOMIYA, HYOGO 6638501, JAPAN; NCI, MAMMALIAN GENET LAB, ABL BASIC RES PROGRAM, FREDERICK CANC RES & DEV CTR, FREDERICK, MD 21702; JAPAN SCI & TECHNOL CORP, CREST, TOKYO, JAPAN  
 COUNTRY OF AUTHOR: JAPAN; USA  
 SOURCE: ONCOGENE, (10 JUN 1999) Vol. 18, No. 23, pp. 3471-3480. Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0950-9232.  
 DOCUMENT TYPE: Article; Journal  
 FILE SEGMENT: LIFE  
 LANGUAGE: English  
 REFERENCE COUNT: 45

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB We have identified and characterized a new calcium/**calmodulin** (Ca2+/CaM) dependent protein **kinase** termed death-associated protein **kinase** 2 (DA PK2) that contains an N-terminal protein **kinase domain** followed by a conserved CaM-binding **domain** with significant homologies to those of **DAP kinase**, a protein **kinase** involved in **apoptosis**. DAPK2 mRNA is expressed abundantly in heart, lung and skeletal muscle. The mapping results indicated that DAPK2 is located in the central region of mouse chromosome 9, *in vitro* **kinase** assay revealed that DAPK2 is autophosphorylated and phosphorylates myosin light chain (MLC) as an exogenous substrate. DAPK2 binds directly to CaM and is activated in a Ca2+/CaM-dependent manner. A constitutively active DAPK2 mutant is

generated by removal of the CaM-binding **domain** (Delta CaM). Treatment of agonists that elevate intracellular Ca<sup>2+</sup>-concentration led to the activation of DAPK2 and transfection studies revealed that DAPK2 is localized in the cytoplasm. Overexpression of DAPK2, but not the **kinase** negative mutant, significantly induced the morphological changes characteristic of **apoptosis**. These results indicate that DAPK2 is an additional member of **DAP kinase** family involved in apoptotic signaling.

L13 ANSWER 16 OF 23 MEDLINE DUPLICATE 7  
 ACCESSION NUMBER: 2000030159 MEDLINE  
 DOCUMENT NUMBER: 20030159 PubMed ID: 10561695  
 TITLE: Developmental changes in distribution of death-associated protein **kinase** mRNAs.  
 AUTHOR: Yamamoto M; Takahashi H; Nakamura T; Hioki T; Nagayama S; Ooashi N; Sun X; Ishii T; Kudo Y; Nakajima-Iijima S; Kimchi A; Uchino S  
 CORPORATE SOURCE: Pharmaceuticals Discovery Laboratory, Yokohama Research Center, Mitsubishi Chemical Corporation, Aoba-ku, Yokohama, Japan.  
 SOURCE: JOURNAL OF NEUROSCIENCE RESEARCH, (1999 Dec 1) 58 (5) 674-83.  
 Journal code: KAC; 7600111. ISSN: 0360-4012.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200001  
 ENTRY DATE: Entered STN: 20000114  
 Last Updated on STN: 20000114  
 Entered Medline: 20000105

AB Death-associated protein **kinase** (DAP-kinase) is Ca(2+)/**calmodulin**-dependent **serine/threonine kinase** that contains ankyrin repeats and the death **domain**. It has been isolated as a positive mediator of interferon-gamma-induced apoptotic **cell death** of HeLa cells. In order to reveal the physiological role of **DAP-kinase**, the tissue distribution and developmental changes in mRNA expression of **DAP-kinase** were investigated by Northern blot and in situ hybridization analyses. **DAP-kinase** mRNA was predominantly expressed in brain and lung. In brain, **DAP-kinase** mRNA had already appeared at embryonic day 13 (E13) and was, thereafter, detected throughout the entire embryonic period. High levels of expression were detected in proliferative and postmitotic regions within cerebral cortex, hippocampus, and cerebellar Purkinje cells. These findings suggest that **DAP-kinase** may play an important role in neurogenesis where a physiological type of **cell death** takes place. The overall expression of **DAP-kinase** mRNA in the brain gradually declined at postnatal stages, and the expression became restricted to hippocampus, in which different expression patterns were observed among rostral, central, and caudal coronal sections, suggesting that **DAP-kinase** may be implicated in some neuronal functions. Furthermore, it was found that the expression of **DAP-kinase** mRNA was increased prior to a certain **cell death** induced by transient forebrain ischemia, indicating a possible relationship between **DAP-kinase** and neuronal **cell death**.  
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L13 ANSWER 17 OF 23 MEDLINE  
 ACCESSION NUMBER: 1999148017 MEDLINE  
 DOCUMENT NUMBER: 99148017 PubMed ID: 10023074

TITLE: Duet is a novel **serine/threonine kinase** with Dbl-Homology (DH) and Pleckstrin-Homology (PH) **domains**.  
 AUTHOR: Kawai T; Sanjo H; Akira S  
 CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan.  
 SOURCE: GENE, (1999 Feb 18) 227 (2) 249-55.  
 Journal code: FOP; 7706761. ISSN: 0378-1119.  
 PUB. COUNTRY: Netherlands  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-AB011422  
 ENTRY MONTH: 199904  
 ENTRY DATE: Entered STN: 19990426  
 Last Updated on STN: 20000303  
 Entered Medline: 19990413

AB We show here the identification of Duet, a novel molecule bearing **serine/threonine kinase**, Dbl-Homology (DH), and Pleckstrin-Homology (PH) **domains**. The **kinase domain** of Duet shows a homology to that of **DAP kinase** that is involved in **apoptosis**, and Duet is autophosphorylated by an in-vitro **kinase** assay. The DH- and PH-**domains** are closely related to those of Trio and Kalirin. Trad mRNA is specifically expressed in skeletal muscle. Duet protein was localized to actin-associated cytoskeletal elements. These data suggest a role of Duet in the cytoskeleton-dependent cell function.

L13 ANSWER 18 OF 23 MEDLINE DUPLICATE 8  
 ACCESSION NUMBER: 1999332304 MEDLINE  
 DOCUMENT NUMBER: 99332304 PubMed ID: 10402466  
 TITLE: **DAP-kinase** participates in TNF-alpha- and Fas-induced **apoptosis** and its function requires the death **domain**.  
 AUTHOR: Cohen O; Inbal B; Kissil J L; Raveh T; Berissi H; Spivak-Kroizaman T; Feinstein E; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: JOURNAL OF CELL BIOLOGY, (1999 Jul 12) 146 (1) 141-8.  
 Journal code: HMV; 0375356. ISSN: 0021-9525.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199908  
 ENTRY DATE: Entered STN: 19990820  
 Last Updated on STN: 19990820  
 Entered Medline: 19990809

AB Death-associated protein (**DAP**)-**kinase** is a calcium/**calmodulin** regulated **serine/threonine kinase** that carries ankyrin repeats, a death **domain**, and is localized to the cytoskeleton. Here, we report that this **kinase** is involved in tumor necrosis factor (TNF)-alpha and Fas-induced **apoptosis**. Expression of **DAP-kinase** antisense RNA protected cells from killing by anti-Fas/APO-1 agonistic antibodies. Deletion of the death **domain** abrogated the apoptotic functions of the **kinase**, thus, documenting for the first time the importance of this protein **domain**. Overexpression of a fragment encompassing the death **domain** of **DAP-kinase** acted as a specific dominant negative mutant that protected cells from TNF-alpha, Fas, and FADD/MORT1-induced cell death. **DAP-kinase** apoptotic function was blocked by bcl-2 as



well as by crmA and p35 inhibitors of caspases, but not by the dominant negative mutants of FADD/MORT1 or of caspase 8. Thus, it functions downstream to the receptor complex and upstream to other caspases. The multidomain structure of this **serine/threonine kinase**, combined with its involvement in **cell death** induced by several different triggers, place **DAP-kinase** at one of the central molecular pathways leading to **apoptosis**.

L13 ANSWER 19 OF 23 MEDLINE

ACCESSION NUMBER: 1999003259 MEDLINE  
DOCUMENT NUMBER: 99003259 PubMed ID: 9786912  
TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.  
AUTHOR: Sanjo H; Kawai T; Akira S  
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421  
ENTRY MONTH: 199812  
ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 20020420  
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic **domains** are related to that of death-associated protein **kinase**, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic **domain** and the C-terminal **domain** that is responsible for regulation of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L13 ANSWER 20 OF 23 MEDLINE

ACCESSION NUMBER: 1998147805 MEDLINE  
DOCUMENT NUMBER: 98147805 PubMed ID: 9488481  
TITLE: ZIP **kinase**, a novel **serine/threonine kinase** which mediates **apoptosis**.  
AUTHOR: Kawai T; Matsumoto M; Takeda K; Sanjo H; Akira S  
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, Nishinomiya, Japan.  
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1998 Mar) 18 (3) 1642-51.  
Journal code: 8109087. ISSN: 0270-7306.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-AB007143; GENBANK-AB007144

ENTRY MONTH: 199803  
ENTRY DATE: Entered STN: 19980326  
Last Updated on STN: 20020420  
Entered Medline: 19980319

AB We have identified a novel **serine/threonine kinase**, designated **ZIP kinase**, which mediates **apoptosis**. **ZIP kinase** contains a leucine zipper structure at its C terminus, in addition to a **kinase domain** at its N terminus. **ZIP kinase** physically binds to ATF4, a member of the activating transcription factor/cyclic AMP-responsive element-binding protein (ATF/CREB) family, through interaction between their leucine zippers. The leucine zipper **domain** is necessary for the homodimerization of **ZIP kinase** as well as for the activation of **kinase**. Immunostaining study showed that **ZIP kinase** localizes in the nuclei. Overexpression of intact **ZIP kinase** but not catalytically inactive **kinase** mutants led to the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting that the **cell death**-inducing activity of **ZIP kinase** depends on its intrinsic **kinase** activity. Interestingly, the catalytic **domain** of **ZIP kinase** is closely related to that of death-associated protein **kinase** (**DAP kinase**), which is a mediator of **apoptosis** induced by gamma interferon. Therefore, both **ZIP** and **DAP kinases** represent a novel **kinase** family, which mediates **apoptosis** through their catalytic activities.

L13 ANSWER 21 OF 23 MEDLINE DUPLICATE 9  
ACCESSION NUMBER: 97224127 MEDLINE  
DOCUMENT NUMBER: 97224127 PubMed ID: 9118961  
TITLE: **DAP-kinase** is a **Ca<sup>2+</sup>/calmodulin**-dependent, cytoskeletal-associated protein **kinase**, with **cell death**-inducing functions that depend on its catalytic activity.  
AUTHOR: Cohen O; Feinstein E; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel.  
SOURCE: EMBO JOURNAL, (1997 Mar 3) 16 (5) 998-1008.  
Journal code: EMB; 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199704  
ENTRY DATE: Entered STN: 19970506  
Last Updated on STN: 19980206  
Entered Medline: 19970422

AB **DAP-kinase** was initially identified as a gene whose anti-sense-mediated reduced expression protected HeLa cells from interferon-gamma-induced programmed **cell death**. It was cloned in our laboratory by a functional gene selection approach. According to its amino acid sequence, this 160 kDa protein was predicted to be a novel type of **calmodulin**-regulated **serine/threonine kinase** which carries ankyrin repeats and the **death domain**. In this work we have shown that the **kinase** was autophosphorylated and capable of phosphorylating an exogenous substrate in a **Ca<sup>2+</sup>/calmodulin**-dependent manner. We proved that **calmodulin** binds directly to the recombinant **kinase**, and generated a constitutively active **kinase** mutant by the deletion of the **calmodulin**-regulatory **domain**. By immunostaining and biochemical fractionations we demonstrated that the **kinase** is localized to the cytoskeleton, in association with the microfilament

system, and mapped a region within the protein which is responsible for binding to the cytoskeleton. Several assays attributed a **cell death** function to the gene. Ectopic expression of wild-type **DAP-kinase** induced the death of target cells, and the killing property depended strictly on the status of the intrinsic **kinase** activity. Conversely, a catalytically inactive mutant that carried a lysine to alanine substitution within the **kinase domain**, displayed dominant-negative features and protected cells from interferon-gamma-induced **cell death**. **DAP-kinase** is therefore a novel cytoskeletal-associated **cell death serine/threonine kinase** whose activation by  $Ca^{2+}$ /**calmodulin** may be linked to the biochemical mechanism underlying the cytoskeletal alterations that occur during **cell death**.

L13 ANSWER 22 OF 23 MEDLINE DUPLICATE 10  
 ACCESSION NUMBER: 97384865 MEDLINE  
 DOCUMENT NUMBER: 97384865 PubMed ID: 9242376  
 TITLE: **DAP-kinase** loss of expression in various carcinoma and B-cell lymphoma cell lines: possible implications for role as tumor suppressor gene.  
 AUTHOR: Kissil J L; Feinstein E; Cohen O; Jones P A; Tsai Y C; Knowles M A; Eydmann M E; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel.  
 CONTRACT NUMBER: CA49758 (NCI)  
 SOURCE: ONCOGENE, (1997 Jul 24) 15 (4) 403-7.  
 Journal code: ONC; 8711562. ISSN: 0950-9232.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199708  
 ENTRY DATE: Entered STN: 19970902  
 Last Updated on STN: 19980206  
 Entered Medline: 19970821

AB **DAP-kinase** is a novel **calmodulin** dependent **serine/threonine kinase** that carries ankyrin repeats and the death **domain**. It was recently isolated, by a functional selection approach of gene cloning, as a positive mediator of programmed **cell death**. In this study the expression of **DAP-kinase** was examined in the cell lines derived from various human neoplasms. **DAP-kinase** mRNA and protein expression were below the limit of detection in eight out of ten neoplastic derived B-cell lines. In six out of 14 examined bladder carcinoma, in three out of five renal cell carcinoma, and in four out of ten tested breast carcinoma cell lines, the **DAP-kinase** protein levels were below detection limits or lower than 1% compared to the positive cell lines. Interestingly, **DAP-kinase** expression could be restored in some of the negative bladder carcinoma and B-cell lines by treatment of cells with 5'-azadeoxycytidine that causes DNA demethylation. The high frequency of loss of **DAP-kinase** expression in human tumor cell lines, and the occasional involvement of methylation in this process raise the possibility that this novel mediator of **cell death** may function as a tumor suppressor gene.

L13 ANSWER 23 OF 23 MEDLINE DUPLICATE 11  
 ACCESSION NUMBER: 1998032978 MEDLINE  
 DOCUMENT NUMBER: 98032978 PubMed ID: 9367156  
 TITLE: **DAP kinase** links the control of **apoptosis** to metastasis.

AUTHOR: Inbal B; Cohen O; Polak-Charcon S; Kopolovic J; Vadai E; Eisenbach L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel.  
 SOURCE: NATURE, (1997 Nov 13) 390 (6656) 180-4.  
 Journal code: NSC; 0410462. ISSN: 0028-0836.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199711  
 ENTRY DATE: Entered STN: 19971224  
 Last Updated on STN: 19971224  
 Entered Medline: 19971125

AB **DAP kinase** is a new type of calcium/calmodulin-dependent enzyme that phosphorylates **serine/threonine** residues on proteins. Its structure contains ankyrin repeats and the 'death' domain, and it is associated with the cell cytoskeleton. The gene encoding **DAP kinase** was initially isolated as a positive mediator of **apoptosis** induced by interferon-gamma, by using a strategy of functional cloning. We have now tested whether this gene has tumour-suppressive activity. We found that lung carcinoma clones, characterized by their highly aggressive metastatic behaviour and originating from two independent murine lung tumours, did not express **DAP kinase**, in contrast to their low-metastatic counterparts. Restoration of **DAP kinase** to physiological levels in high-metastatic Lewis carcinoma cells suppressed their ability to form lung metastases after intravenous injection into syngeneic mice, and delayed local tumour growth in a foreign 'microenvironment'. Conversely, in vivo selection of rare lung lesions following injection into syngeneic mice of low-metastatic Lewis carcinoma cells or of **DAP kinase** transfectants, was associated with loss of **DAP kinase** expression. In situ TUNEL staining of tumour sections revealed that **DAP kinase** expression from the transgene raised the incidence of **apoptosis** in vivo. **DAP-kinase** transfectants also showed increased sensitivity in vitro to apoptotic stimuli, of the sort encountered by metastasizing cells at different stages of malignancy. We propose that loss of **DAP kinase** expression provides a unique mechanism that links suppression of **apoptosis** to metastasis.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULIN  
 L2 110146 S CALMODULIN  
 L3 342878 S SERINE OR THREONINE  
 L4 73725 S L3 AND KINASE  
 L5 6021 S L2 AND L4  
 L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
 L7 391 S L5 AND L6  
 L8 195 S HUMAN AND L7  
 L9 1023024 S DOMAIN?  
 L10 111 S L7 AND L9  
 L11 345 S DAP(A) KINASE?  
 L12 72 S L10 AND L11  
 L13 23 DUP REM L12 (49 DUPLICATES REMOVED)

=> s carboxy(w) terminal or carboxy (w)end or C-terminal

3 FILES SEARCHED...

L14 255022 CARBOXY(W) TERMINAL OR CARBOXY (W) END OR C-TERMINAL

=> s l10 and l14

L15 34 L10 AND L14

=> dup rem l15

PROCESSING COMPLETED FOR L15

L16 17 DUP REM L15 (17 DUPLICATES REMOVED)

=> d 1-17 ibib ab

L16 ANSWER 1 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2002:89428 SCISEARCH

THE GENUINE ARTICLE: 513UP

TITLE: DAP **kinase** activity is critical for  
C-2-ceramide-induced **apoptosis** in PC12 cells

AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S;  
Uchino S

CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,  
Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,  
Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi  
Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut  
Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan

COUNTRY OF AUTHOR: Japan

SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.  
1, pp. 139-147.

Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD,  
OXFORD OX2 ONE, OXON, ENGLAND.

ISSN: 0014-2956.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 41

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. DAP **kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30  $\mu$ M C-2-ceramide, both the total (assayed in the presence of  $\text{Ca}^{2+}$ /**calmodulin**) and  $\text{Ca}^{2+}$ /**calmodulin** -independent (assayed in the presence of EGTA) DAP **kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30  $\mu$ M C-2-ceramide, the  $\text{Ca}^{2+}$ /**calmodulin** independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated DAP **kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase DAP **kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type DAP **kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive DAP **kinase** mutant and a construct containing the death **domain** and C-terminal tail of DAP **kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that DAP **kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic

DAP **kinase** activity is critical for ceramide-induced  
**apoptosis**.

L16 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:43345 HCAPLUS  
DOCUMENT NUMBER: 136:319709  
TITLE: Transcriptional profiling reveals global defects in  
energy metabolism, lipoprotein, and bile acid  
synthesis and transport with reversal by leptin  
treatment in Ob/ob mouse liver  
AUTHOR(S): Liang, Chien-Ping; Tall, Alan R.  
CORPORATE SOURCE: Division of Molecular Medicine, Department of  
Medicine, Columbia University, New York, NY, 10032,  
USA  
SOURCE: Journal of Biological Chemistry (2001), 276(52),  
49066-49076  
CODEN: JBCHA3; ISSN: 0021-9258  
PUBLISHER: American Society for Biochemistry and Molecular  
Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Leptin, a hormone secreted by adipose tissue, has been shown to have a  
major influence on hepatic lipid and lipoprotein metab. To characterize  
changes in lipid and lipoprotein gene expression in mouse liver,  
suppression subtractive hybridization and cDNA microarray anal. were used  
to identify mRNAs differentially expressed after leptin treatment of ob/ob  
mice. Ob/ob mice showed a profound decrease in mRNAs encoding genes  
controlling bile acid synthesis and transport as well as a variety of  
apolipoprotein genes and hepatic lipase with reversal upon leptin  
administration, suggesting that leptin coordinately regulates high d.  
lipoprotein and bile salt metab. Leptin administration also resulted in  
decreased expression of genes involved in fatty acid and cholesterol  
synthesis, glycolysis, gluconeogenesis, and urea synthesis, and increased  
expression of genes mediating fatty acid oxidn., ATP synthesis, and  
oxidant defenses. The changes in mRNA expression are consistent with a  
switch in energy metab. from glucose utilization and fatty acid synthesis  
to fatty acid oxidn. and increased respiration. The latter changes may  
produce oxidant stress, explaining the unexpected finding that leptin  
induces a battery of genes involved in antioxidant defenses. Expression  
cluster anal. revealed responses of several sets of genes that were  
kinetically linked. Thus, the mRNA levels of genes involved in fatty acid  
and cholesterol synthesis are rapidly (<1 h) repressed by leptin  
administration, in assocn. with an acute decrease in plasma insulin levels  
and decreased sterol regulator element-binding protein-1 expression. In  
contrast, genes participating in fatty acid oxidn. and ketogenesis were  
induced more slowly (24 h), following an increase in expression of their  
common regulatory factor, peroxisome proliferator-activated receptor  
.alpha.. However, the regulation of genes involved in high d. lipoprotein  
and bile salt metab. shows complex kinetics and is likely to be mediated  
by novel transcription factors.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 17 MEDLINE

ACCESSION NUMBER: 2001169641 MEDLINE  
DOCUMENT NUMBER: 21167344 PubMed ID: 11268041  
TITLE: The DAP **kinase** family of pro-apoptotic proteins:  
novel players in the apoptotic game.  
AUTHOR: Kogel D; Prehn J H; Scheidtmann K H  
CORPORATE SOURCE: Interdisciplinary Center for Clinical Research (IZKF),  
University of Munster, Germany.. koegel@uni-muenster.de  
SOURCE: BIOESSAYS, (2001 Apr) 23 (4) 352-8. Ref: 47

Journal code: 9YY; 8510851. ISSN: 0265-9247.

PUB. COUNTRY: England: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200105

ENTRY DATE: Entered STN: 20010604  
Last Updated on STN: 20010604  
Entered Medline: 20010531

AB The DAP (Death Associated Protein) **kinase** family is a novel subfamily of pro-apoptotic **serine/threonine kinases**. All five DAP **kinase** family members identified to date are ubiquitously expressed in various tissues and are capable of inducing **apoptosis**. The sequence homology of the five **kinases** is largely restricted to the N-terminal **kinase domain**. In contrast, the adjacent **C-terminal** regions are very diverse and link individual family members to specific signal transduction pathways. There is increasing evidence that DAP **kinase** family members are involved in both extrinsic and intrinsic pathways of **apoptosis** and may play a role in tumor progression. This review will focus on structural composition and subcellular localization of DAP **kinase** family members and on signal transduction pathways leading to their activation. Potential mechanisms of DAP **kinase** family-mediated **apoptosis** will be discussed. BioEssays 23:352-358, 2001. Copyright 2001 John Wiley & Sons, Inc.

L16 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:775265 HCAPLUS

DOCUMENT NUMBER: 136:132090

TITLE: Investigation of differentially expressed genes during the development of mouse cerebellum

AUTHOR(S): Kagami, Yoshihiro; Furuichi, Teiichi

CORPORATE SOURCE: Laboratory for Molecular Neurogenesis, Brain Science Institute, RIKEN, Wako, 351-0198, Japan

SOURCE: Gene Expression Patterns (2001), 1(1), 39-59  
CODEN: GEPEAD; ISSN: 1567-133X

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Before the discovery of DNA microarray and DNA chip technol., the expression of only a small no. of genes could be analyzed at a time. Currently, such technol. allows us the simultaneous anal. of a large no. of genes to systematically monitor their expression patterns that may be assocd. with various biol. phenomena. We utilized the Affymetrix GeneChip MullK to analyze the gene expression profile in developing mouse cerebellum to assist in the understanding of the genetic basis of cerebellar development in mice. Our anal. showed 81.6% (10.321/12.654) of the genes represented on the GeneChip were expressed in the postnatal cerebellum, and among those, 8.7% (897/10.321) were differentially expressed with more than a two-fold change in their max. and min. expression levels during the developmental time course. Further anal. of the differentially expressed genes that were clustered in terms of their expression patterns and the function of their encoded products revealed an aspect of the genetic foundation that lies beneath the cellular events and neural network formation that takes place during the development of the mouse cerebellum.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 5 OF 17 MEDLINE DUPLICATE 1  
 ACCESSION NUMBER: 2001434353 MEDLINE  
 DOCUMENT NUMBER: 21214809 PubMed ID: 11313698  
 TITLE: DAP-**kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.  
 AUTHOR: Cohen O; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
 Ref: 39  
 Journal code: C7U; 9437445. ISSN: 1350-9047.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200108  
 ENTRY DATE: Entered STN: 20010806  
 Last Updated on STN: 20010806  
 Entered Medline: 20010802

AB DAP-**kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of DAP-**kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine-rich C-terminal** tail, spanning the last 17 amino acids of the protein. A link between DAP-**kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-**kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-**kinase** was also studied experimentally in mouse model systems where the re-introduction of DAP-**kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of DAP-**kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with DAP-**kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L16 ANSWER 6 OF 17 MEDLINE  
 ACCESSION NUMBER: 2000187596 MEDLINE  
 DOCUMENT NUMBER: 20187596 PubMed ID: 10722720  
 TITLE: Activation of MST/Krs and c-Jun N-terminal **kinases** by different signaling pathways during cytotrienin A-induced **apoptosis**.  
 AUTHOR: Watabe M; Takeya H; Onose R; Osada H



CORPORATE SOURCE: Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi,  
Saitama 351-0198, Japan.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12)  
8766-71.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200004  
ENTRY DATE: Entered STN: 20000505  
Last Updated on STN: 20020420  
Entered Medline: 20000427

AB We found that antitumor drugs such as cytotrienin A, camptothecin, taxol, and 5-fluorouracil induced the activation of a 36-kDa protein **kinase** (p36 myelin basic protein (MBP) **kinase**) during **apoptosis** in human promyelocytic leukemia HL-60 cells. This p36 MBP **kinase**, which phosphorylates MBP in an in-gel **kinase** assay, results from the caspase-3-mediated proteolytic cleavage of MST/Krs protein, a mammalian Ste20-like **serine/threonine kinase**. Herein the correlation between cytotrienin A-induced **apoptosis** and the activation of MST/Krs proteins was examined in human tumor cell lines, including leukemia-, lung-, epidermoid-, cervix-, stomach-, and brain-derived cell lines. In cytotrienin A-sensitive cell lines, we observed a strong activation of p36 MBP **kinase** by cleavage of the **C-terminal regulatory domain** of full-length MST/Krs proteins by caspase-3. When the **kinase** -inactive mutant form of MST/Krs protein was overexpressed in cytotrienin A-sensitive HL-60 cells, the cytotrienin A-induced **apoptosis** was partially inhibited. Because cytotrienin A also activated c-Jun N-terminal **kinase**, we examined the effect of the expression of dominant negative c-Jun on cytotrienin A-induced **apoptosis**. The expression of dominant negative c-Jun also partially inhibited cytotrienin A-induced **apoptosis**. Furthermore, coexpression of **kinase** -inactive MST/Krs protein and dominant negative c-Jun completely suppressed cytotrienin A-induced **apoptosis**. These findings suggest that the proteolytic activation of MST/Krs and c-Jun N-terminal **kinase** activation are involved in cytotrienin A-induced **apoptosis** in human tumor cell lines.

L16 ANSWER 7 OF 17 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2000144081 MEDLINE  
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.  
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.  
Journal code: PV3; 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200003  
ENTRY DATE: Entered STN: 20000330  
Last Updated on STN: 20000330  
Entered Medline: 20000323  
AB Death-associated protein **kinase** (DAP-**kinase**) is a

Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L16 ANSWER 8 OF 17 MEDLINE DUPLICATE 3  
 ACCESSION NUMBER: 2000094983 MEDLINE  
 DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
 TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.  
 AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420  
 Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(+2)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**.

DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L16 ANSWER 9 OF 17 MEDLINE DUPLICATE 4  
 ACCESSION NUMBER: 2000481058 MEDLINE  
 DOCUMENT NUMBER: 20431384 PubMed ID: 10976872  
 TITLE: Activation of calcium/**calmodulin** regulated **kinases**.  
 AUTHOR: Wilmann M; Gautel M; Mayans O  
 CORPORATE SOURCE: EMBL, Hamburg, Germany.. wilmanns@embl-hamburg.de  
 SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (2000 Jul) 46 (5) 883-94.  
 Journal code: BNA; 9216789. ISSN: 0145-5680.  
 PUB. COUNTRY: France  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200010  
 ENTRY DATE: Entered STN: 20001019  
 Last Updated on STN: 20001019  
 Entered Medline: 20001012

AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are regulated by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death**, **cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium/**calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**, myosin light chain **kinase**). As a common element, all these **kinases** contain a regulatory tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle proteins twitchin and titin in the autoinhibited conformation, show how this regulatory tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium/**calmodulin** binding. In addition, members of this family are regulated by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional regulatory

subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the regulatory tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L16 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:430068 BIOSIS

DOCUMENT NUMBER: PREV2000000430068

TITLE: Activation of calcium/**calmodulin** regulated **kinases**.

AUTHOR(S): Wilmanns, Mathias (1); Gautel, Mathias; Mayans, Olga

CORPORATE SOURCE: (1) EMBL c/o DESY, Notkestrasse 85, D-22603, Hamburg Germany

SOURCE: Cellular and Molecular Biology (Noisy-Le-Grand), (July, 2000) Vol. 46, No. 5, pp. 883-894. print.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are regulated by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death**, **cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium / **calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**, myosin light chain **kinase**). As a common element, all these **kinases** contain a regulatory tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle protein twitchin and titin in the autoinhibited conformation, show how this regulatory tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium / **calmodulin** binding. In addition, members of this family are regulated by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional regulatory subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the regulatory tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L16 ANSWER 11 OF 17 MEDLINE

ACCESSION NUMBER: 1999430101 MEDLINE

DOCUMENT NUMBER: 99430101 PubMed ID: 10498871

TITLE: Requirement of protein **kinase** (Krs/MST) activation for MT-21-induced **apoptosis**.

AUTHOR: Watabe M; Kakeya H; Osada H

CORPORATE SOURCE: Laboratory of Antibiotics, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.

SOURCE: ONCOGENE, (1999 Sep 16) 18 (37) 5211-20.

Journal code: 8711562. ISSN: 0950-9232.

PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199910  
ENTRY DATE: Entered STN: 19991101  
Last Updated on STN: 20020420  
Entered Medline: 19991021

AB Fas is a well characterized **apoptosis**-inducing factor. One of our synthetic compounds, MT-21, induced **apoptosis** in human leukemia HL-60 cells similar to Fas. MT-21 activated caspase-3, an important cysteine aspartic protease for **apoptosis** induction. MT-21 also activated c-Jun-NH2-terminal **kinase** (JNK), a member of mitogen activated protein **kinase** (MAPK) superfamily that is involved in the regulation of cell growth, differentiation and **cell death**. Moreover, MT-21 treatment resulted in the activation of a 36 kDa **kinase** which uses myelin basic protein (MBP) as a substrate. However, MAPK and p38 were not activated by treatment with MT-21. The 36 kDa MBP **kinase** was shown to be a proteolytic product derived from the Krs protein with a molecular weight of 60 kDa. The Krs protein is a Ser/Thr protein **kinase** whose activity is enhanced by digestion of its **C-terminal** regulatory **domain** by caspase-3. When a **kinase**-inactive mutant form of Krs protein was overexpressed in HL-60 cells, JNK activation and **apoptosis** induction by MT-21 were suppressed. Furthermore, overexpression of dominant negative c-Jun also suppressed **apoptosis** induction by MT-21. These findings indicate that MT-21 induces **apoptosis** by the activation of JNK via the Krs protein, which is activated by caspase cleavage.

L16 ANSWER 12 OF 17 MEDLINE

ACCESSION NUMBER: 1999164089 MEDLINE  
DOCUMENT NUMBER: 99164089 PubMed ID: 10064589  
TITLE: **Apoptosis** inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation.  
AUTHOR: Asada M; Yamada T; Ichijo H; Delia D; Miyazono K; Fukumuro K; Mizutani S  
CORPORATE SOURCE: Department of Virology, The National Children's Medical Research Center, 3-35-31, Taishido, Setagaya-ku, Tokyo, 154, Japan.  
SOURCE: EMBO JOURNAL, (1999 Mar 1) 18 (5) 1223-34.  
Journal code: EMB; 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199904  
ENTRY DATE: Entered STN: 19990511  
Last Updated on STN: 20000303  
Entered Medline: 19990429

AB p21(Cip1/WAF1) inhibits cell-cycle progression by binding to G1 cyclin/CDK complexes and proliferating cell nuclear antigen (PCNA) through its N- and **C-terminal domains**, respectively. The cell-cycle inhibitory activity of p21(Cip1/WAF1) is correlated with its nuclear localization. Here, we report a novel cytoplasmic localization of p21(Cip1/WAF1) in peripheral blood monocytes (PBMs) and in U937 cells undergoing monocytic differentiation by in vitro treatment with vitamin D3 or ectopic expression of p21(Cip1/WAF1), and analyze the biological consequences of this cytoplasmic expression. U937 cells which exhibit nuclear p21(Cip1/WAF1) demonstrated G1 cell-cycle arrest and subsequently differentiated into monocytes. The latter event was associated with a cytoplasmic expression of nuclear p21(Cip1/WAF1), concomitantly with a resistance to various apoptogenic stimuli. Biochemical analysis showed that cytoplasmic p21(Cip1/WAF1) forms a complex with the **apoptosis**

signal-regulating **kinase** 1 (ASK1) and inhibits stress-activated MAP **kinase** cascade. Expression of a deletion mutant of p21(Cip1/WAF1) lacking the nuclear localization signal (DeltaNLS-p21) did not induce cell cycle arrest nor monocytic differentiation, but led to an **apoptosis**-resistant phenotype, mediated by binding to and inhibition of the stress-activated ASK1 activity. Thus, cytoplasmic p21(Cip1/WAF1) itself acted as an inhibitor of **apoptosis**. Our findings highlight the different functional roles of p21(Cip1/WAF1), which are determined by its intracellular distribution and are dependent on the stage of differentiation.

L16 ANSWER 13 OF 17 MEDLINE

ACCESSION NUMBER: 2000029738 MEDLINE  
 DOCUMENT NUMBER: 20029738 PubMed ID: 10561491  
 TITLE: Hematopoietic lineage cell specific protein 1 associates with and down-regulates protein **kinase** CK2.  
 AUTHOR: Ruzzene M; Brunati A M; Sarno S; Donella-Deana A; Pinna L A  
 CORPORATE SOURCE: Dipartimento di Chimica Biologica and Centro per lo Studio delle Biomembrane del CNR, University of Padova, Viale G. Colombo, 335121, Padova, Italy.  
 SOURCE: FEBS LETTERS, (1999 Nov 12) 461 (1-2) 32-6.  
 Journal code: 0155157. ISSN: 0014-5793.  
 PUB. COUNTRY: Netherlands  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199912  
 ENTRY DATE: Entered STN: 20000113  
 Last Updated on STN: 20020420  
 Entered Medline: 19991214

AB The catalytic (alpha) subunit of protein **kinase** CK2 and the hematopoietic specific protein 1 (HS1) display opposite effects on Ha-ras induced fibroblast transformation, by enhancing and counteracting it, respectively. Here we show the occurrence of physical association between HS1 and CK2alpha as judged from both far Western blot and plasmon resonance (BIAcore) analysis. Association of HS1 with CK2alpha is drastically reduced by the deletion of the HS1 C-terminal region (403-486) containing an SH3 **domain**. HS1, but not its deletion mutant HS1 Delta324-393, lacking a sequence similar to an acidic stretch of the regulatory beta-subunit of CK2, inhibits **calmodulin** phosphorylation by CK2alpha. These data indicate that HS1 physically interacts with CK2alpha and down-regulates its activity by a mechanism similar to the beta-subunit.

L16 ANSWER 14 OF 17 MEDLINE

ACCESSION NUMBER: 1999003259 MEDLINE  
 DOCUMENT NUMBER: 99003259 PubMed ID: 9786912  
 TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.  
 AUTHOR: Sanjo H; Kawai T; Akira S  
 CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421  
 ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 20020420  
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic domains are related to that of death-associated protein kinase, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic domain and the C-terminal domain that is responsible for regulation of kinase activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro kinase assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the kinase activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L16 ANSWER 15 OF 17 MEDLINE

ACCESSION NUMBER: 1998211933 MEDLINE  
DOCUMENT NUMBER: 98211933 PubMed ID: 9545236  
TITLE: Caspase-mediated activation and induction of **apoptosis** by the mammalian Ste20-like kinase Mst1.  
AUTHOR: Graves J D; Gotoh Y; Draves K E; Ambrose D; Han D K; Wright M; Chernoff J; Clark E A; Krebs E G  
CORPORATE SOURCE: Department of Immunology, University of Washington Medical Center, Seattle, WA 98109, USA.  
CONTRACT NUMBER: GM37905 (NIGMS)  
GM42508 (NIGMS)  
SOURCE: EMBO JOURNAL, (1998 Apr 15) 17 (8) 2224-34.  
Journal code: 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199806  
ENTRY DATE: Entered STN: 19980708  
Last Updated on STN: 20020420  
Entered Medline: 19980624

AB Mst1 is a ubiquitously expressed **serine-threonine kinase**, homologous to the budding yeast Ste20, whose physiological regulation and cellular function are unknown. In this paper we show that Mst1 is specifically cleaved by a caspase 3-like activity during **apoptosis** induced by either cross-linking CD95/Fas or by staurosporine treatment. CD95/Fas-induced cleavage of Mst1 was blocked by the cysteine protease inhibitor ZVAD-fmk, the more selective caspase inhibitor DEVD-CHO and by the viral serpin CrmA. Caspase-mediated cleavage of Mst1 removes the C-terminal regulatory domain and correlates with an increase in Mst1 activity in vivo, consistent with caspase-mediated cleavage activating Mst1. Overexpression of either wild-type Mst1 or a truncated mutant induces morphological changes characteristic of **apoptosis**. Furthermore, exogenously expressed Mst1 is cleaved, indicating that Mst1 can activate caspases that result in its cleavage. Kinase-dead Mst1 did not induce morphological alterations and was not cleaved upon overexpression, indicating that Mst1 must be catalytically active in order to mediate these effects. Mst1 activates MKK6, p38 MAPK, MKK7 and SAPK in co-transfection assays, suggesting that Mst1 may activate these pathways. Our findings suggest the existence of a positive feedback loop involving Mst1, and possibly the SAPK and p38 MAPK pathways, which serves to amplify

the apoptotic response.

L16 ANSWER 16 OF 17 MEDLINE

ACCESSION NUMBER: 1998416694 MEDLINE  
DOCUMENT NUMBER: 98416694 PubMed ID: 9739089  
TITLE: Crystal structure of JNK3: a **kinase** implicated in neuronal **apoptosis**.  
AUTHOR: Xie X; Gu Y; Fox T; Coll J T; Fleming M A; Markland W; Caron P R; Wilson K P; Su M S  
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, MA 02139-4211, USA.  
SOURCE: STRUCTURE, (1998 Aug 15) 6 (8) 983-91.  
JOURNAL code: B31; 9418985. ISSN: 0969-2126.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: PDB-1JNK  
ENTRY MONTH: 199812  
ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 20000303  
Entered Medline: 19981208

AB BACKGROUND: The c-Jun N-terminal **kinases** (JNKs) are members of the mitogen-activated protein (MAP) **kinase** family, and regulate signal transduction in response to environmental stress. Activation and nuclear localization of JNK3, a neuronal-specific isoform of JNK, has been associated with hypoxic and ischemic damage of CA1 neurons in the hippocampus. Knockout mice lacking JNK3 showed reduced **apoptosis** of hippocampal neurons and reduced seizure induced by kainic acid, a glutamate-receptor agonist. Thus, JNK3 may be important in the pathology of neurological disorders and is of significant medical interest. RESULTS: We report here the structure of unphosphorylated JNK3 in complex with adenylyl imidodiphosphate, an ATP analog. JNK3 has a typical **kinase** fold, with the ATP-binding site situated within a cleft between the N- and C-terminal domains. In contrast to other known MAP **kinase** structures, the ATP-binding site of JNK3 is well ordered; the glycine-rich nucleotide-binding sequence forms a beta-strand-turn-beta-strand structure over the nucleotide. Unphosphorylated JNK3 assumes an open conformation, in which the N- and C-terminal domains are twisted apart relative to their positions in cAMP-dependent protein **kinase**. The rotation leads to the misalignment of some of the catalytic residues. The phosphorylation lip of JNK3 partially blocks the substrate-binding site. CONCLUSIONS: This is the first JNK structure to be determined, providing a unique opportunity to compare structures from the three MAP **kinase** subfamilies. The structure reveals atomic-level details of the shape of JNK3 and the interactions between the **kinase** and the nucleotide. The misalignment of catalytic residues and occlusion of the active site by the phosphorylation lip may account for the low activity of unphosphorylated JNK3. The structure provides a framework for understanding the substrate specificity of different JNK isoforms, and should aid the design of selective JNK3 inhibitors.

L16 ANSWER 17 OF 17 MEDLINE

ACCESSION NUMBER: 97474480 MEDLINE  
DOCUMENT NUMBER: 97474480 PubMed ID: 9335504  
TITLE: Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1.  
AUTHOR: Kretzschmar M; Doody J; Massague J  
CORPORATE SOURCE: Cell Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.  
SOURCE: NATURE, (1997 Oct 9) 389 (6651) 618-22.



Journal code: NSC; 0410462. ISSN: 0028-0836.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199711  
ENTRY DATE: Entered STN: 19971224  
Last Updated on STN: 20000303  
Entered Medline: 19971103

AB The growth factor TGF-beta, bone morphogenetic proteins (BMPs) and related factors regulate cell proliferation, differentiation and **apoptosis**, controlling the development and maintenance of most tissues. Their signals are transmitted through the phosphorylation of the tumour-suppressor SMAD proteins by receptor protein **serine/threonine kinases** (RS/TKs), leading to the nuclear accumulation and transcriptional activity of SMAD proteins. Here we report that Smad1, which mediates BMP signals, is also a target of mitogenic growth-factor signalling through epidermal growth factor and hepatocyte growth factor receptor protein tyrosine **kinases** (RTKs). Phosphorylation occurs at specific **serines** within the region linking the inhibitory and effector **domains** of Smad1, and is catalysed by the Erk family of mitogen-activated protein **kinases**. In contrast to the BMP-stimulated phosphorylation of Smad1, which affects **carboxy-terminal serines** and induces nuclear accumulation of Smad1, Erk-mediated phosphorylation specifically inhibits the nuclear accumulation of Smad1. Thus, Smad1 receives opposing regulatory inputs through RTKs and RS/TKs, and it is this balance that determines the level of Smad1 activity in the nucleus, and so possibly the role of Smad1 in the control of cell fate.

=> s "DAP"  
L17 10019 "DAP"

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULIN  
L2 110146 S CALMODULIN  
L3 342878 S SERINE OR THREONINE  
L4 73725 S L3 AND KINASE  
L5 6021 S L2 AND L4  
L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
L7 391 S L5 AND L6  
L8 195 S HUMAN AND L7  
L9 1023024 S DOMAIN?  
L10 111 S L7 AND L9  
L11 345 S DAP(A) KINASE?  
L12 72 S L10 AND L11  
L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL  
L15 34 S L10 AND L14  
L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
L17 10019 S "DAP"

=> s l16 and l17  
L18 6 L16 AND L17

=> d 1-6 ibib ab

L18 ANSWER 1 OF 6 MEDLINE  
 ACCESSION NUMBER: 2001434353 MEDLINE  
 DOCUMENT NUMBER: 21214809 PubMed ID: 11313698  
 TITLE: **DAP-kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.  
 AUTHOR: Cohen O; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
 Ref: 39  
 Journal code: C7U; 9437445. ISSN: 1350-9047.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200108  
 ENTRY DATE: Entered STN: 20010806  
 Last Updated on STN: 20010806  
 Entered Medline: 20010802

AB **DAP-kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of **DAP-kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine-rich C-terminal** tail, spanning the last 17 amino acids of the protein. A link between **DAP-kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of **DAP-kinase's** 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of **DAP-kinase** was also studied experimentally in mouse model systems where the re-introduction of **DAP-kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP-kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with **DAP-kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L18 ANSWER 2 OF 6 MEDLINE  
 ACCESSION NUMBER: 2001169641 MEDLINE  
 DOCUMENT NUMBER: 21167344 PubMed ID: 11268041  
 TITLE: The **DAP kinase** family of pro-apoptotic

proteins: novel players in the apoptotic game.  
 AUTHOR: Kogel D; Prehn J H; Scheidtmann K H  
 CORPORATE SOURCE: Interdisciplinary Center for Clinical Research (IZKF),  
 University of Munster, Germany.. koegel@uni-muenster.de  
 SOURCE: BIOESSAYS, (2001 Apr) 23 (4) 352-8. Ref: 47  
 Journal code: 9YY; 8510851. ISSN: 0265-9247.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200105  
 ENTRY DATE: Entered STN: 20010604  
 Last Updated on STN: 20010604  
 Entered Medline: 20010531

AB The **DAP** (Death Associated Protein) **kinase** family is a novel subfamily of pro-apoptotic **serine/threonine kinases**. All five **DAP kinase** family members identified to date are ubiquitously expressed in various tissues and are capable of inducing **apoptosis**. The sequence homology of the five **kinases** is largely restricted to the N-terminal **kinase domain**. In contrast, the adjacent **C-terminal** regions are very diverse and link individual family members to specific signal transduction pathways. There is increasing evidence that **DAP kinase** family members are involved in both extrinsic and intrinsic pathways of **apoptosis** and may play a role in tumor progression. This review will focus on structural composition and subcellular localization of **DAP kinase** family members and on signal transduction pathways leading to their activation. Potential mechanisms of **DAP kinase** family-mediated **apoptosis** will be discussed. BioEssays 23:352-358, 2001. Copyright 2001 John Wiley & Sons, Inc.

L18 ANSWER 3 OF 6 MEDLINE  
 ACCESSION NUMBER: 2000144081 MEDLINE  
 DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
 TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.  
 AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.  
 Journal code: PV3; 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200003  
 ENTRY DATE: Entered STN: 20000330  
 Last Updated on STN: 20000330  
 Entered Medline: 20000323

AB Death-associated protein **kinase** (**DAP-kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP-kinase**-derived fragments that

could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP-kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP-kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of **DAP-kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP-kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP-kinase** apoptotic function that does not affect the catalytic activity.

L18 ANSWER 4 OF 6 MEDLINE  
 ACCESSION NUMBER: 2000094983 MEDLINE  
 DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
 TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.  
 AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420  
 Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to **DAP kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from **DAP kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, **DAP kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the

CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of **DAP kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by **DAP kinase**. Possible functional connections between **DAP kinase** and DRP-1 are discussed.

L18 ANSWER 5 OF 6 MEDLINE  
 ACCESSION NUMBER: 1999003259 MEDLINE  
 DOCUMENT NUMBER: 99003259 PubMed ID: 9786912  
 TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.  
 AUTHOR: Sanjo H; Kawai T; Akira S  
 CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421  
 ENTRY MONTH: 199812  
 ENTRY DATE: Entered STN: 19990115  
 Last Updated on STN: 20020420  
 Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic **domains** are related to that of death-associated protein **kinase**, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic **domain** and the **C-terminal domain** that is responsible for regulation of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L18 ANSWER 6 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)  
 ACCESSION NUMBER: 2002:89428 SCISEARCH  
 THE GENUINE ARTICLE: 513UP  
 TITLE: **DAP kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells  
 AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S  
 CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,

Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,  
Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi  
Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut  
Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan

COUNTRY OF AUTHOR:

SOURCE:

EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.  
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OXFORD OX2 ONE, OXON, ENGLAND.

ISSN: 0014-2956.

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Article; Journal

LANGUAGE:

English

REFERENCE COUNT:

41

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. **DAP kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30  $\mu$ M C-2-ceramide, both the total (assayed in the presence of  $\text{Ca}^{2+}$ /calmodulin) and  $\text{Ca}^{2+}$ /calmodulin-independent (assayed in the presence of EGTA) **DAP kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30  $\mu$ M C-2-ceramide, the  $\text{Ca}^{2+}$ /calmodulin independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated **DAP kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase **DAP kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type **DAP kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive **DAP kinase** mutant and a construct containing the death domain and C-terminal tail of **DAP kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that **DAP kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic **DAP kinase** activity is critical for ceramide-induced **apoptosis**.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULAIN  
L2 110146 S CALMODULIN  
L3 342878 S SERINE OR THREONINE  
L4 73725 S L3 AND KINASE  
L5 6021 S L2 AND L4  
L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
L7 391 S L5 AND L6  
L8 195 S HUMAN AND L7  
L9 1023024 S DOMAIN?  
L10 111 S L7 AND L9  
L11 345 S DAP (A) KINASE?

L12 72 S L10 AND L11  
 L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
 L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL  
 L15 34 S L10 AND L14  
 L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
 L17 10019 S "DAP"  
 L18 6 S L16 AND L17

=> s "zip"  
 L19 4269 "ZIP"

=> l16 and l19  
 L16 IS NOT A RECOGNIZED COMMAND  
 The previous command name entered was not recognized by the system.  
 For a list of commands available to you in the current file, enter  
 "HELP COMMANDS" at an arrow prompt (=>).

=> s l16 and l19  
 L20 2 L16 AND L19

=> d 1-2 ibib ab

L20 ANSWER 1 OF 2 MEDLINE  
 ACCESSION NUMBER: 2000094983 MEDLINE  
 DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
 TITLE: Death-associated protein **kinase**-related protein  
 1, a novel **serine/threonine**  
**kinase** involved in **apoptosis**.  
 AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
 Science, Rehovot 76100, Israel.  
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.  
 Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420  
 Entered Medline: 20000214

AB In this study we describe the identification and structure-function  
 analysis of a novel death-associated protein (DAP) **kinase**  
 -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin**  
 (CaM)-regulated **serine threonine kinase**  
 which shows high degree of homology to DAP **kinase**. The region of  
 homology spans the catalytic **domain** and the CaM-regulatory  
 region, whereas the remaining **C-terminal** part of the  
 protein differs completely from DAP **kinase** and displays no  
 homology to any known protein. The catalytic **domain** is also  
 homologous to the recently identified **ZIP kinase** and  
 to a lesser extent to the catalytic **domains** of DRAK1 and -2.  
 Thus, DAP **kinase** DRP-1, **ZIP kinase**, and  
 DRAK1/2 together form a novel subfamily of **serine/**  
**threonine kinases**. DRP-1 is localized to the cytoplasm,  
 as shown by immunostaining and cellular fractionation assays. It binds to  
 CaM, undergoes autophosphorylation, and phosphorylates an exogenous  
 substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The  
 truncated protein, deleted of the CaM-regulatory **domain**, was  
 converted into a constitutively active **kinase**. Ectopically  
 expressed DRP-1 induced **apoptosis** in various types of cells.  
 Cell killing by DRP-1 was dependent on two features: the status of the

catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L20 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2002:89428 SCISEARCH

THE GENUINE ARTICLE: 513UP

TITLE: DAP **kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells

AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S

CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida, Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan

COUNTRY OF AUTHOR: Japan

SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No. 1, pp. 139-147.

Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 ONE, OXON, ENGLAND.

ISSN: 0014-2956.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 41

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. DAP **kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30  $\mu$ M C-2-ceramide, both the total (assayed in the presence of Ca<sup>2+</sup>/calmodulin) and Ca<sup>2+</sup>/calmodulin-independent (assayed in the presence of EGTA) DAP **kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30  $\mu$ M C-2-ceramide, the Ca<sup>2+</sup>/calmodulin independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated DAP **kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase DAP **kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type DAP **kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive DAP **kinase** mutant and a construct containing the death **domain** and **C-terminal** tail of DAP **kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that DAP **kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic DAP **kinase** activity is critical for ceramide-induced



apoptosis.

=> s "DRP-1"  
L21 98 "DRP-1"

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULAIN  
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L9 1023024 S DOMAIN?  
L10 111 S L7 AND L9  
L11 345 S DAP(A) KINASE?  
L12 72 S L10 AND L11  
L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL  
L15 34 S L10 AND L14  
L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
L17 10019 S "DAP"  
L18 6 S L16 AND L17  
L19 4269 S "ZIP"  
L20 2 S L16 AND L19  
L21 98 S "DRP-1"

=> s l16 and l21  
L22 1 L16 AND L21

=> d all

L22 ANSWER 1 OF 1 MEDLINE  
AN 2000094983 MEDLINE  
DN 20094983 PubMed ID: 10629061  
TI Death-associated protein **kinase**-related protein 1, a novel  
**serine/threonine kinase** involved in  
**apoptosis**.  
AU Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
CS Department of Molecular Genetics, Weizmann Institute of Science, Rehovot  
76100, Israel.  
SO MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.  
Journal code: 8109087. ISSN: 0270-7306.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200002  
ED Entered STN: 20000229  
Last Updated on STN: 20020420  
Entered Medline: 20000214  
AB In this study we describe the identification and structure-function  
analysis of a novel death-associated protein (DAP) **kinase**  
-related protein, **DRP-1**. **DRP-1** is  
a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine**

**threonine kinase** which shows high degree of homology to **DAP kinase**. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from **DAP kinase** and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified **ZIP kinase** and to a lesser extent to the catalytic domains of **DRAK1** and **-2**. Thus, **DAP kinase** **DRP-1**, **ZIP kinase**, and **DRAK1/2** together form a novel subfamily of **serine/threonine kinases**.

**DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active **kinase**. Ectopically expressed **DRP-1** induced **apoptosis** in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of **DAP kinase** encompassing the death domain was found to block **apoptosis** induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by **DAP kinase**. Possible functional connections between **DAP kinase** and **DRP-1** are discussed.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't  
Amino Acid Sequence

**\*Apoptosis**

Base Sequence

Breast Neoplasms

**Catalytic Domain**

Cell Line

Cloning, Molecular

Gene Library

Kidney

Molecular Sequence Data

Phylogeny

**\*Protein-Serine-Threonine Kinases: CH, chemistry**

**\*Protein-Serine-Threonine Kinases: GE, genetics**

**Protein-Serine-Threonine Kinases: ME, metabolism**

RNA, Messenger: GE, genetics

Recombinant Proteins: CH, chemistry

Recombinant Proteins: ME, metabolism

Sequence Alignment

Sequence Homology, Amino Acid

Spleen: ME, metabolism

Transcription, Genetic

Translation, Genetic

Tumor Cells, Cultured

CN 0 (RNA, Messenger); 0 (Recombinant Proteins); EC 2.7.1.- (DRAK1 protein); EC 2.7.1.- (DRAK2 protein); EC 2.7.1.- (Protein-Serine-Threonine Kinases); EC 2.7.1.- (death-associated protein kinase-related protein 1)

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

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L19 4269 S "ZIP"  
L20 2 S L16 AND L19  
L21 98 S "DRP-1"  
L22 1 S L16 AND L21

=> e kimchi a/au

E1 2 KIMCHE L/AU  
E2 1 KIMCHE N/AU  
E3 484 --> KIMCHI A/AU  
E4 8 KIMCHI A \*/AU  
E5 1 KIMCHI A N/AU  
E6 131 KIMCHI ADI/AU  
E7 1 KIMCHI ADY/AU  
E8 5 KIMCHI B/AU  
E9 2 KIMCHI BRACHA/AU  
E10 24 KIMCHI D/AU  
E11 1 KIMCHI DVORA/AU  
E12 13 KIMCHI E/AU

=> s e3

L23 484 "KIMCHI A"/AU

=> s l16 and l23

L24 3 L16 AND L23

=> dup rem l24

PROCESSING COMPLETED FOR L24

L25 3 DUP REM L24 (0 DUPLICATES REMOVED)

=> d 1-3 ibib ab

L25 ANSWER 1 OF 3

MEDLINE

ACCESSION NUMBER: 2001434353 MEDLINE

DOCUMENT NUMBER: 21214809 PubMed ID: 11313698

TITLE: DAP-kinase: from functional gene cloning to establishment of its role in apoptosis and cancer.

AUTHOR: Cohen O; Kimchi A

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of

SOURCE: Science, Rehovot 76100, Israel.  
 CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
 Ref: 39  
 Journal code: C7U; 9437445. ISSN: 1350-9047.

PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200108  
 ENTRY DATE: Entered STN: 20010806  
 Last Updated on STN: 20010806  
 Entered Medline: 20010802

AB DAP-kinase is a pro-apoptotic Ca(2+) **calmodulin**  
 -regulated **serine/threonine kinase** that  
 participates in a wide array of apoptotic systems initiated by  
 interferon-gamma, TNF-alpha, activated Fas, and detachment from  
 extracellular matrix. It was isolated by an unbiased functional approach  
 to gene cloning aimed at hitting central mediators of the apoptotic  
 process. This 160 Kd protein **kinase** is localized to actin  
 microfilaments and carries interesting modules such as ankyrin repeats and  
 the death **domain**. The death promoting effects of DAP-  
**kinase** depend on its intact catalytic activity, the correct  
 intracellular localization, and on the presence of the death  
**domain**. A few mechanisms restrain the killing effects of the  
 protein in healthy cells. The enzyme's active site is negatively  
 controlled by an adjacent CaM regulatory **domain** whose effect is  
 relieved by binding to Ca(2+)-activated **calmodulin**. A second  
 mode of autoinhibition engages the **serine**-rich C-  
**terminal** tail, spanning the last 17 amino acids of the protein. A  
 link between DAP-**kinase** and cancer has been established. It was  
 found that the mRNA and protein expression is frequently lost in various  
 human cancer cell lines. Analysis of the methylation status of DAP-  
**kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed  
 high incidence of hypermethylation in several human carcinomas and B cell  
 malignancies. The anti-tumorigenic effect of DAP-**kinase** was also  
 studied experimentally in mouse model systems where the re-introduction of  
 DAP-**kinase** into highly metastatic mouse lung carcinoma cells who  
 had lost the protein, strongly reduced their metastatic capacity. Thus, it  
 appears that loss of DAP-**kinase** confers a selective advantage to  
 cancer cells and may play a causative role in tumor progression. A few  
 novel **kinases** sharing high homology in their catalytic  
**domains** with DAP-**kinase** have been recently identified  
 constituting altogether a novel family of death promoting **serine**  
 /**threonine kinases**.

L25 ANSWER 2 OF 3 MEDLINE  
 ACCESSION NUMBER: 2000144081 MEDLINE  
 DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
 TITLE: A functional genetic screen identifies regions at the  
**C-terminal** tail and death-**domain**  
 of death-associated protein **kinase** that are  
 critical for its proapoptotic activity.

AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; **Kimchi**  
**A**

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
 Science, Rehovot 76100, Israel.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE  
 UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.  
 Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200003  
ENTRY DATE: Entered STN: 20000330  
Last Updated on STN: 20000330  
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L25 ANSWER 3 OF 3 MEDLINE  
ACCESSION NUMBER: 2000094983 MEDLINE  
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.  
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200002  
ENTRY DATE: Entered STN: 20000229  
Last Updated on STN: 20020420  
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of

homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

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L5      6021 S L2 AND L4
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L7      391 S L5 AND L6
L8      195 S HUMAN AND L7
L9      1023024 S DOMAIN?
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L12     72 S L10 AND L11
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L15     34 S L10 AND L14
L16     17 DUP REM L15 (17 DUPLICATES REMOVED)
L17     10019 S "DAP"
L18     6 S L16 AND L17
L19     4269 S "ZIP"
L20     2 S L16 AND L19
L21     98 S "DRP-1"
L22     1 S L16 AND L21
        E KIMCHI A/AU
L23     484 S E3
L24     3 S L16 AND L23
L25     3 DUP REM L24 (0 DUPLICATES REMOVED)

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L27 7 L23 AND DRP##

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L28 ANSWER 1 OF 2 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2001216755 MEDLINE  
DOCUMENT NUMBER: 21153208 PubMed ID: 11230133  
TITLE: Autophosphorylation restrains the apoptotic activity of  
**DRP-1** kinase by controlling dimerization and  
calmodulin binding.  
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein  
M; Ziv T; Admon A; **Kimchi A**  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
Science, Rehovot 76100, Israel.  
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.  
Journal code: 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: England: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200104  
ENTRY DATE: Entered STN: 20010425  
Last Updated on STN: 20020420  
Entered Medline: 20010419  
AB **DRP-1** is a pro-apoptotic Ca<sup>2+</sup>/calmodulin (CaM)-regulated  
serine/threonine kinase, recently isolated as a novel member of the  
DAP-kinase family of proteins. It contains a short extra-catalytic tail  
required for homodimerization. Here we identify a novel regulatory  
mechanism that controls its pro-apoptotic functions. It comprises a single  
autophosphorylation event mapped to Ser308 within the CaM regulatory  
domain. A negative charge at this site reduces both the binding to CaM and  
the formation of **DRP-1** homodimers. Conversely, the  
dephosphorylation of Ser308, which takes place in response to activated  
Fas or tumour necrosis factor- $\alpha$  death receptors, increases the  
formation of **DRP-1** dimers, facilitates the binding to CaM and  
activates the pro-apoptotic effects of the protein. Thus, the process of  
enzyme activation is controlled by two unlocking steps that must work in  
concert, i.e. dephosphorylation, which probably weakens the electrostatic  
interactions between the CaM regulatory domain and the catalytic cleft,  
and homodimerization. This mechanism of negative autophosphorylation  
provides a safety barrier that restrains the killing effects of  
**DRP-1**, and a target for efficient activation of the kinase by  
various apoptotic stimuli.

L28 ANSWER 2 OF 2 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2000094983 MEDLINE  
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
TITLE: Death-associated protein kinase-related protein 1, a novel  
serine/threonine kinase involved in apoptosis.  
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
Science, Rehovot 76100, Israel.  
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.

Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420  
 Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) kinase-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to DAP kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP kinase **DRP-1**, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP kinase encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP kinase. Possible functional connections between DAP kinase and **DRP-1** are discussed.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULIN  
 L2 110146 S CALMODULIN  
 L3 342878 S SERINE OR THREONINE  
 L4 73725 S L3 AND KINASE  
 L5 6021 S L2 AND L4  
 L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
 L7 391 S L5 AND L6  
 L8 195 S HUMAN AND L7  
 L9 1023024 S DOMAIN?  
 L10 111 S L7 AND L9  
 L11 345 S DAP(A) KINASE?  
 L12 72 S L10 AND L11  
 L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
 L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL  
 L15 34 S L10 AND L14  
 L16 17 DUP REM L15 (17 DUPLICATES REMOVED)



L17 10019 S "DAP"  
 L18 6 S L16 AND L17  
 L19 4269 S "ZIP"  
 L20 2 S L16 AND L19  
 L21 98 S "DRP-1"  
 L22 1 S L16 AND L21  
 E KIMCHI A/AU  
 L23 484 S E3  
 L24 3 S L16 AND L23  
 L25 3 DUP REM L24 (0 DUPLICATES REMOVED)  
 L26 1 S L25 AND DRP##  
 L27 7 S L23 AND DRP##  
 L28 2 DUP REM L27 (5 DUPLICATES REMOVED)

=> s 123 and 117  
 L29 81 L23 AND L17

=> s 129 and 114  
 L30 18 L29 AND L14

=> dup rem 130  
 PROCESSING COMPLETED FOR L30  
 L31 6 DUP REM L30 (12 DUPLICATES REMOVED)

=> d 1-6 ibib ab

L31 ANSWER 1 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)  
 ACCESSION NUMBER: 2002:92210 SCISEARCH  
 THE GENUINE ARTICLE: 514CW  
 TITLE: Death-associated protein (**DAP**) kinase plays a  
 central role in ceramide-induced apoptosis in cultured  
 hippocampal neurons  
 AUTHOR: Pelled D; Raveh T; Riebeling C; Fridkin M; Berissi H;  
 Futerman A H (Reprint); **Kimchi A**  
 CORPORATE SOURCE: Weizmann Inst Sci, Dept Biol Chem, IL-76100 Rehovot,  
 Israel (Reprint); Weizmann Inst Sci, Dept Mol Genet,  
 IL-76100 Rehovot, Israel; Weizmann Inst Sci, Dept Organ  
 Chem, IL-76100 Rehovot, Israel  
 COUNTRY OF AUTHOR: Israel  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (18 JAN 2002) Vol. 277,  
 No. 3, pp. 1957-1961.  
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC,  
 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.  
 ISSN: 0021-9258.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 21

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Treatment of cultured hippocampal neurons with high concentrations of  
 short-chain acyl ceramide derivatives, such as N-hexanoyl-D-sphingosine  
 (C-6-Cer), results in apoptotic cell death. We now show that  
 death-associated protein (**DAP**) kinase plays an important role in  
 mediating this effect. Upon incubation with C-6-Cer, **DAP** kinase  
 levels are elevated as early as 1 h after treatment, reaching levels  
 2-3-fold higher than untreated cells after 4 h. Neurons cultured from  
**DAP** kinase-deficient mice were significantly less sensitive to  
 apoptosis induced by C-6-Cer or by ceramide generated by high  
 concentrations of nerve growth factor. A peptide corresponding to the 17  
 amino acids at the C terminus of **DAP** kinase protected wild type  
 neurons from C-6-Cer-induced death and from death induced by the addition  
 of exogenous bacterial neutral sphingomyelinase, whereas a scrambled  
 peptide had no protective effect, implying that the **DAP** kinase

**C-terminal** tail inhibits the function of **DAP** kinase. Together, these data demonstrate that **DAP** kinase plays a central role in ceramide-induced cell death in neurons, but the pathway in which **DAP** kinase is involved is not the only one via which ceramide can induce apoptosis.

L31 ANSWER 2 OF 6 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2001434353 MEDLINE  
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698  
TITLE: **DAP**-kinase: from functional gene cloning to establishment of its role in apoptosis and cancer.  
AUTHOR: Cohen O; **Kimchi A**  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
Ref: 39  
Journal code: C7U; 9437445. ISSN: 1350-9047.  
PUB. COUNTRY: England: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200108  
ENTRY DATE: Entered STN: 20010806  
Last Updated on STN: 20010806  
Entered Medline: 20010802

AB **DAP**-kinase is a pro-apoptotic Ca(2+) calmodulin-regulated serine/threonine kinase that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein kinase is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death domain. The death promoting effects of **DAP**-kinase depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death domain. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory domain whose effect is relieved by binding to Ca(2+)-activated calmodulin. A second mode of autoinhibition engages the serine-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between **DAP**-kinase and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of **DAP**-kinase's 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of **DAP**-kinase was also studied experimentally in mouse model systems where the re-introduction of **DAP**-kinase into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP**-kinase confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel kinases sharing high homology in their catalytic domains with **DAP**-kinase have been recently identified constituting altogether a novel family of death promoting serine/threonine kinases.

L31 ANSWER 3 OF 6 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2000144081 MEDLINE  
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-domain of

death-associated protein kinase that are critical for its proapoptotic activity.

AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; **Kimchi A**

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States

JOURNAL; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000330  
Last Updated on STN: 20000330  
Entered Medline: 20000323

AB Death-associated protein kinase (**DAP**-kinase) is a Ca(+2)/calmodulin-regulated serine/threonine kinase with a multidomain structure that participates in apoptosis induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP**-kinase-derived fragments that could protect cells from apoptosis by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP**-kinase cDNA in HeLa cells and treated these cells with IFN-gamma to induce apoptosis. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP**-kinase-dependent tumor necrosis factor-alpha-induced apoptosis. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death domain, and the **C-terminal** tail of **DAP**-kinase. Molecular modeling of the complete death domain provided a structural basis for the function of the death-domain-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal** serine-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP**-kinase, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP**-kinase apoptotic function that does not affect the catalytic activity.

L31 ANSWER 4 OF 6 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000094983 MEDLINE

DOCUMENT NUMBER: 20094983 PubMed ID: 10629061

TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.

AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.

SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States

JOURNAL; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200002

ENTRY DATE: Entered STN: 20000229

Last Updated on STN: 20020420

Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) kinase-related protein, **DRP-1**. **DRP-1** is a 42-kDa  $\text{Ca}^{2+}$ /calmodulin (**CaM**)-regulated serine threonine kinase which shows high degree of homology to **DAP** kinase. The region of homology spans the catalytic domain and the **CaM**-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from **DAP** kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified **ZIP** kinase and to a lesser extent to the catalytic domains of **DRAK1** and **-2**. Thus, **DAP** kinase **DRP-1**, **ZIP** kinase, and **DRAK1/2** together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to **CaM**, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a  $\text{Ca}^{2+}$ /**CaM**-dependent manner. The truncated protein, deleted of the **CaM**-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the **CaM**-regulatory region could override the indispensable role of the **C-terminal** tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of **DAP** kinase encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by **DAP** kinase. Possible functional connections between **DAP** kinase and **DRP-1** are discussed.

L31 ANSWER 5 OF 6 MEDLINE  
ACCESSION NUMBER: 2000079262 MEDLINE  
DOCUMENT NUMBER: 20079262 PubMed ID: 10611228  
TITLE: A novel form of **DAP5** protein accumulates in apoptotic cells as a result of caspase cleavage and internal ribosome entry site-mediated translation.  
AUTHOR: Henis-Korenblit S; Strumpf N L; Goldstaub D; **Kimchi**  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Jan) 20 (2) 496-506.  
PUB. COUNTRY: United States  
JOURNAL; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200001  
ENTRY DATE: Entered STN: 20000204  
Last Updated on STN: 20000204  
Entered Medline: 20000127

AB Death-associated protein 5 (**DAP5**) (also named **p97** and **NAT1**) is a member of the translation initiation factor 4G (**eIF4G**) family that lacks the **eIF4E** binding site. It was previously implicated in apoptosis, based on the finding that a dominant negative fragment of the protein protected against cell death. Here we address its function and two distinct levels of regulation during apoptosis that affect the protein both at translational and posttranslational levels. **DAP5** protein was found to be cleaved at a single caspase cleavage site at position 790, in response to activated **Fas** or **p53**, yielding a **C-terminal** truncated protein of 86

kDa that is capable of generating complexes with eIF4A and eIF3. Interestingly, while the overall translation rate in apoptotic cells was reduced by 60 to 70%, in accordance with the simultaneous degradation of the two major mediators of cap-dependent translation, eIF4GI and eIF4GII, the translation rate of DAP5 protein was selectively maintained. An internal ribosome entry site (IRES) element capable of directing the translation of a reporter gene when subcloned into a bicistronic vector was identified in the 5' untranslated region of DAP5 mRNA. While cap-dependent translation from this transfected vector was reduced during Fas-induced apoptosis, the translation via the DAP5 IRES was selectively maintained. Addition of recombinant DAP5/p97 or DAP5/p86 to cell-free systems enhanced preferentially the translation through the DAP5 IRES, whereas neutralization of the endogenous DAP5 in reticulocyte lysates by adding a dominant negative DAP5 fragment interfered with this translation. The DAP5/p86 apoptotic form was more potent than DAP5/p97 in these functional assays. Altogether, the data suggest that DAP5 is a caspase-activated translation factor which mediates cap-independent translation at least from its own IRES, thus generating a positive feedback loop responsible for the continuous translation of DAP5 during apoptosis.

L31 ANSWER 6 OF 6 MEDLINE DUPLICATE 4  
 ACCESSION NUMBER: 97184487 MEDLINE  
 DOCUMENT NUMBER: 97184487 PubMed ID: 9032289  
 TITLE: **DAP-5**, a novel homolog of eukaryotic translation initiation factor 4G isolated as a putative modulator of gamma interferon-induced programmed cell death.  
 AUTHOR: Levy-Strumpf N; Deiss L P; Berissi H; **Kimchi A**  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel.  
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1997 Mar) 17 (3) 1615-25. Journal code: NGY; 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-X89713  
 ENTRY MONTH: 199703  
 ENTRY DATE: Entered STN: 19970327  
 Last Updated on STN: 19970327  
 Entered Medline: 19970314

AB A functional approach to gene cloning was applied to HeLa cells in an attempt to isolate cDNA fragments which convey resistance to gamma interferon (IFN-gamma)-induced programmed cell death. One of the rescued cDNAs, described in this work, was a fragment of a novel gene, named **DAP-5**. Analysis of a **DAP-5** full-length cDNA clone revealed that it codes for a 97-kDa protein that is highly homologous to eukaryotic translation initiation factor 4G (eIF4G, also known as p220). According to its deduced amino acid sequence, this novel protein lacks the N-terminal region of eIF4G responsible for association with the cap binding protein eIF4E. The N-terminal part of **DAP-5** has 39% identity and 63% similarity to the central region of mammalian p220. Its **C-terminal** part is less homologous to the corresponding region of p220, suggesting that it may possess unique functional properties. The rescued **DAP-5** cDNA fragment which conveyed resistance to IFN-gamma-induced cell death was expressed from the vector in the sense orientation. Intriguingly, it comprised part of the coding region which corresponds to the less conserved **C-terminal** part of **DAP-5** and directed the synthesis of a 28-kDa miniprotein. The miniprotein exerted a dual effect on HeLa cells. Low levels of expression protected the cells from IFN-gamma-induced programmed cell death, while high levels of expression were not compatible

with continuous cell growth. The relevance of **DAP**-5 protein to possible changes in a cell's translational machinery during programmed cell death and growth arrest is discussed.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

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L1      0 S CALMODULAIN
L2     110146 S CALMODULIN
L3     342878 S SERINE OR THREONINE
L4      73725 S L3 AND KINASE
L5      6021 S L2 AND L4
L6     422053 S (CELL (A) DEATH) OR APOPTOSIS
L7      391 S L5 AND L6
L8      195 S HUMAN AND L7
L9     1023024 S DOMAIN?
L10     111 S L7 AND L9
L11     345 S DAP(A) KINASE?
L12      72 S L10 AND L11
L13      23 DUP REM L12 (49 DUPLICATES REMOVED)
L14     255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15      34 S L10 AND L14
L16      17 DUP REM L15 (17 DUPLICATES REMOVED)
L17     10019 S "DAP"
L18      6 S L16 AND L17
L19     4269 S "ZIP"
L20      2 S L16 AND L19
L21     98 S "DRP-1"
L22      1 S L16 AND L21
          E KIMCHI A/AU
L23     484 S E3
L24      3 S L16 AND L23
L25      3 DUP REM L24 (0 DUPLICATES REMOVED)
L26      1 S L25 AND DRP##
L27      7 S L23 AND DRP##
L28      2 DUP REM L27 (5 DUPLICATES REMOVED)
L29     81 S L23 AND L17
L30     18 S L29 AND L14
L31      6 DUP REM L30 (12 DUPLICATES REMOVED)
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=> s l16 and regulat?

L32 15 L16 AND REGULAT?

=> dup rem l32

PROCESSING COMPLETED FOR L32

L33 15 DUP REM L32 (0 DUPLICATES REMOVED)

=> d 1-15 ibib ab

L33 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:43345 HCAPLUS

DOCUMENT NUMBER: 136:319709

TITLE: Transcriptional profiling reveals global defects in energy metabolism, lipoprotein, and bile acid synthesis and transport with reversal by leptin treatment in Ob/ob mouse liver

AUTHOR(S): Liang, Chien-Ping; Tall, Alan R.

CORPORATE SOURCE: Division of Molecular Medicine, Department of

Medicine, Columbia University, New York, NY, 10032,  
USA

SOURCE: Journal of Biological Chemistry (2001), 276(52),  
49066-49076

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular  
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Leptin, a hormone secreted by adipose tissue, has been shown to have a major influence on hepatic lipid and lipoprotein metab. To characterize changes in lipid and lipoprotein gene expression in mouse liver, suppression subtractive hybridization and cDNA microarray anal. were used to identify mRNAs differentially expressed after leptin treatment of ob/ob mice. Ob/ob mice showed a profound decrease in mRNAs encoding genes controlling bile acid synthesis and transport as well as a variety of apolipoprotein genes and hepatic lipase with reversal upon leptin administration, suggesting that leptin coordinately **regulates** high d. lipoprotein and bile salt metab. Leptin administration also resulted in decreased expression of genes involved in fatty acid and cholesterol synthesis, glycolysis, gluconeogenesis, and urea synthesis, and increased expression of genes mediating fatty acid oxidn., ATP synthesis, and oxidant defenses. The changes in mRNA expression are consistent with a switch in energy metab. from glucose utilization and fatty acid synthesis to fatty acid oxidn. and increased respiration. The latter changes may produce oxidant stress, explaining the unexpected finding that leptin induces a battery of genes involved in antioxidant defenses. Expression cluster anal. revealed responses of several sets of genes that were kinetically linked. Thus, the mRNA levels of genes involved in fatty acid and cholesterol synthesis are rapidly (<1 h) repressed by leptin administration, in assocn. with an acute decrease in plasma insulin levels and decreased sterol **regulator** element-binding protein-1 expression. In contrast, genes participating in fatty acid oxidn. and ketogenesis were induced more slowly (24 h), following an increase in expression of their common **regulatory** factor, peroxisome proliferator-activated receptor .alpha.. However, the **regulation** of genes involved in high d. lipoprotein and bile salt metab. shows complex kinetics and is likely to be mediated by novel transcription factors.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:775265 HCAPLUS

DOCUMENT NUMBER: 136:132090

TITLE: Investigation of differentially expressed genes during  
the development of mouse cerebellum

AUTHOR(S): Kagami, Yoshihiro; Furuichi, Teiichi

CORPORATE SOURCE: Laboratory for Molecular Neurogenesis, Brain Science  
Institute, RIKEN, Wako, 351-0198, Japan

SOURCE: Gene Expression Patterns (2001), 1(1), 39-59

CODEN: GEPEAD; ISSN: 1567-133X

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Before the discovery of DNA microarray and DNA chip technol., the expression of only a small no. of genes could be analyzed at a time. Currently, such technol. allows us the simultaneous anal. of a large no. of genes to systematically monitor their expression patterns that may be assocd. with various biol. phenomena. We utilized the Affymetrix GeneChip MullK to analyze the gene expression profile in developing mouse cerebellum to assist in the understanding of the genetic basis of

cerebellar development in mice. Our anal. showed 81.6% (10.321/12.654) of the genes represented on the GeneChip were expressed in the postnatal cerebellum, and among those, 8.7% (897/10.321) were differentially expressed with more than a two-fold change in their max. and min. expression levels during the developmental time course. Further anal. of the differentially expressed genes that were clustered in terms of their expression patterns and the function of their encoded products revealed an aspect of the genetic foundation that lies beneath the cellular events and neural network formation that takes place during the development of the mouse cerebellum.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 15 MEDLINE  
 ACCESSION NUMBER: 2001434353 MEDLINE  
 DOCUMENT NUMBER: 21214809 PubMed ID: 11313698  
 TITLE: DAP-kinase: from functional gene cloning to establishment of its role in **apoptosis** and cancer.  
 AUTHOR: Cohen O; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
 Ref: 39  
 Journal code: C7U; 9437445. ISSN: 1350-9047.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200108  
 ENTRY DATE: Entered STN: 20010806  
 Last Updated on STN: 20010806  
 Entered Medline: 20010802

AB DAP-kinase is a pro-apoptotic Ca(2+) **calmodulin-regulated serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of DAP-kinase depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM **regulatory domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine-rich C-terminal** tail, spanning the last 17 amino acids of the protein. A link between DAP-kinase and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-kinase's 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-kinase was also studied experimentally in mouse model systems where the re-introduction of DAP-kinase into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of DAP-kinase



confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with DAP-**kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L33 ANSWER 4 OF 15 MEDLINE  
ACCESSION NUMBER: 2000187596 MEDLINE  
DOCUMENT NUMBER: 20187596 PubMed ID: 10722720  
TITLE: Activation of MST/Krs and c-Jun N-terminal **kinases** by different signaling pathways during cytotrienin A-induced **apoptosis**.  
AUTHOR: Watabe M; Kakeya H; Onose R; Osada H  
CORPORATE SOURCE: Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8766-71.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200004  
ENTRY DATE: Entered STN: 20000505  
Last Updated on STN: 20020420  
Entered Medline: 20000427

AB We found that antitumor drugs such as cytotrienin A, camptothecin, taxol, and 5-fluorouracil induced the activation of a 36-kDa protein **kinase** (p36 myelin basic protein (MBP) **kinase**) during **apoptosis** in human promyelocytic leukemia HL-60 cells. This p36 MBP **kinase**, which phosphorylates MBP in an in-gel **kinase** assay, results from the caspase-3-mediated proteolytic cleavage of MST/Krs protein, a mammalian Ste20-like **serine/threonine kinase**. Herein the correlation between cytotrienin A-induced **apoptosis** and the activation of MST/Krs proteins was examined in human tumor cell lines, including leukemia-, lung-, epidermoid-, cervix-, stomach-, and brain-derived cell lines. In cytotrienin A-sensitive cell lines, we observed a strong activation of p36 MBP **kinase** by cleavage of the **C-terminal regulatory domain** of full-length MST/Krs proteins by caspase-3. When the **kinase**-inactive mutant form of MST/Krs protein was overexpressed in cytotrienin A-sensitive HL-60 cells, the cytotrienin A-induced **apoptosis** was partially inhibited. Because cytotrienin A also activated c-Jun N-terminal **kinase**, we examined the effect of the expression of dominant negative c-Jun on cytotrienin A-induced **apoptosis**. The expression of dominant negative c-Jun also partially inhibited cytotrienin A-induced **apoptosis**. Furthermore, coexpression of **kinase**-inactive MST/Krs protein and dominant negative c-Jun completely suppressed cytotrienin A-induced **apoptosis**. These findings suggest that the proteolytic activation of MST/Krs and c-Jun N-terminal **kinase** activation are involved in cytotrienin A-induced **apoptosis** in human tumor cell lines.

L33 ANSWER 5 OF 15 MEDLINE  
ACCESSION NUMBER: 2000144081 MEDLINE  
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.  
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of

SOURCE: Science, Rehovot 76100, Israel.  
 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE  
 UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.  
 Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200003  
 ENTRY DATE: Entered STN: 20000330  
 Last Updated on STN: 20000330  
 Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a  
 Ca(+2)/**calmodulin-regulated serine/**  
**threonine kinase** with a multidomain structure that  
 participates in **apoptosis** induced by a variety of signals. To  
 identify regions in this protein that are critical for its proapoptotic  
 activity, we performed a genetic screen on the basis of functional  
 selection of short DAP-**kinase**-derived fragments that could  
 protect cells from **apoptosis** by acting in a dominant-negative  
 manner. We expressed a library of randomly fragmented DAP-**kinase**  
 cDNA in HeLa cells and treated these cells with IFN-gamma to induce  
**apoptosis**. Functional cDNA fragments were recovered from cells  
 that survived the selection, and those in the sense orientation were  
 examined further in a secondary screen for their ability to protect cells  
 from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced  
**apoptosis**. We isolated four biologically active peptides that  
 mapped to the ankyrin repeats, the "linker" region, the death  
**domain**, and the **C-terminal** tail of DAP-  
**kinase**. Molecular modeling of the complete death **domain**  
 provided a structural basis for the function of the death-**domain**  
 -derived fragment by suggesting that the protective fragment constitutes a  
 distinct substructure. The last fragment, spanning the **C-**  
**terminal serine**-rich tail, defined a new  
**regulatory** region. Ectopic expression of the tail peptide (17  
 amino acids) inhibited the function of DAP-**kinase**, whereas  
 removal of this region from the complete protein caused enhancement of the  
 killing activity, indicating that the **C-terminal** tail  
 normally plays a negative **regulatory** role. Altogether, this  
 unbiased screen highlighted functionally important regions in the protein  
 and revealed an additional level of **regulation** of DAP-  
**kinase** apoptotic function that does not affect the catalytic  
 activity.

L33 ANSWER 6 OF 15 MEDLINE

ACCESSION NUMBER: 2000094983 MEDLINE  
 DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
 TITLE: Death-associated protein **kinase**-related protein  
 1, a novel **serine/threonine**  
**kinase** involved in **apoptosis**.

AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
 Science, Rehovot 76100, Israel.

SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.  
 Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420

Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase** -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-**regulated serine threonine** **kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-**regulatory** region, whereas the remaining C-**terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-**regulatory domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the C-**terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-**regulatory** region could override the indispensable role of the C-**terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L33 ANSWER 7 OF 15 MEDLINE  
ACCESSION NUMBER: 2000481058 MEDLINE  
DOCUMENT NUMBER: 20431384 PubMed ID: 10976872  
TITLE: Activation of calcium/**calmodulin** **regulated kinases**.  
AUTHOR: Wilmann M; Gautel M; Mayans O  
CORPORATE SOURCE: EMBL, Hamburg, Germany.. wilmanns@embl-hamburg.de  
SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (2000 Jul) 46 (5) 883-94.  
Journal code: BNA; 9216789. ISSN: 0145-5680.  
PUB. COUNTRY: France  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200010  
ENTRY DATE: Entered STN: 20001019  
Last Updated on STN: 20001019  
Entered Medline: 20001012

AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine** **kinases** that are **regulated** by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death**, **cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium/**calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**,

myosin light chain **kinase**). As a common element, all these **kinases** contain a **regulatory** tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle proteins twitchin and titin in the autoinhibited conformation, show how this **regulatory** tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium/**calmodulin** binding. In addition, members of this family are **regulated** by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional **regulatory** subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the **regulatory** tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L33 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:430068 BIOSIS

DOCUMENT NUMBER: PREV200000430068

TITLE: Activation of calcium/**calmodulin regulated kinases**.

AUTHOR(S): Wilmanns, Mathias (1); Gautel, Mathias; Mayans, Olga  
CORPORATE SOURCE: (1) EMBL c/o DESY, Notkestrasse 85, D-22603, Hamburg Germany

SOURCE: Cellular and Molecular Biology (Noisy-Le-Grand), (July, 2000) Vol. 46, No. 5, pp. 883-894. print.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are **regulated** by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death**, cell motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium / **calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**, myosin light chain **kinase**). As a common element, all these **kinases** contain a **regulatory** tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle protein twitchin and titin in the autoinhibited conformation, show how this **regulatory** tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium / **calmodulin** binding. In addition, members of this family are **regulated** by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional **regulatory** subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the **regulatory** tail is entirely released

("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L33 ANSWER 9 OF 15 MEDLINE

ACCESSION NUMBER: 1999430101 MEDLINE  
DOCUMENT NUMBER: 99430101 PubMed ID: 10498871  
TITLE: Requirement of protein **kinase** (Krs/MST) activation for MT-21-induced **apoptosis**.  
AUTHOR: Watabe M; Kakeya H; Osada H  
CORPORATE SOURCE: Laboratory of Antibiotics, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.  
SOURCE: ONCOGENE, (1999 Sep 16) 18 (37) 5211-20.  
Journal code: 8711562. ISSN: 0950-9232.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199910  
ENTRY DATE: Entered STN: 19991101  
Last Updated on STN: 20020420  
Entered Medline: 19991021

AB Fas is a well characterized **apoptosis**-inducing factor. One of our synthetic compounds, MT-21, induced **apoptosis** in human leukemia HL-60 cells similar to Fas. MT-21 activated caspase-3, an important cysteine aspartic protease for **apoptosis** induction. MT-21 also activated c-Jun-NH2-terminal **kinase** (JNK), a member of mitogen activated protein **kinase** (MAPK) superfamily that is involved in the **regulation** of cell growth, differentiation and **cell death**. Moreover, MT-21 treatment resulted in the activation of a 36 kDa **kinase** which uses myelin basic protein (MBP) as a substrate. However, MAPK and p38 were not activated by treatment with MT-21. The 36 kDa MBP **kinase** was shown to be a proteolytic product derived from the Krs protein with a molecular weight of 60 kDa. The Krs protein is a Ser/Thr protein **kinase** whose activity is enhanced by digestion of its **C-terminal regulatory domain** by caspase-3. When a **kinase** -inactive mutant form of Krs protein was overexpressed in HL-60 cells, JNK activation and **apoptosis** induction by MT-21 were suppressed. Furthermore, overexpression of dominant negative c-Jun also suppressed **apoptosis** induction by MT-21. These findings indicate that MT-21 induces **apoptosis** by the activation of JNK via the Krs protein, which is activated by caspase cleavage.

L33 ANSWER 10 OF 15 MEDLINE

ACCESSION NUMBER: 1999164089 MEDLINE  
DOCUMENT NUMBER: 99164089 PubMed ID: 10064589  
TITLE: **Apoptosis** inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation.  
AUTHOR: Asada M; Yamada T; Ichijo H; Delia D; Miyazono K; Fukumuro K; Mizutani S  
CORPORATE SOURCE: Department of Virology, The National Children's Medical Research Center, 3-35-31, Taishido, Setagaya-ku, Tokyo, 154, Japan.  
SOURCE: EMBO JOURNAL, (1999 Mar 1) 18 (5) 1223-34.  
Journal code: EMB; 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199904  
ENTRY DATE: Entered STN: 19990511

Last Updated on STN: 20000303

Entered Medline: 19990429

AB p21(Cip1/WAF1) inhibits cell-cycle progression by binding to G1 cyclin/CDK complexes and proliferating cell nuclear antigen (PCNA) through its N- and C-terminal domains, respectively. The cell-cycle inhibitory activity of p21(Cip1/WAF1) is correlated with its nuclear localization. Here, we report a novel cytoplasmic localization of p21(Cip1/WAF1) in peripheral blood monocytes (PBMs) and in U937 cells undergoing monocytic differentiation by in vitro treatment with vitamin D3 or ectopic expression of p21(Cip1/WAF1), and analyze the biological consequences of this cytoplasmic expression. U937 cells which exhibit nuclear p21(Cip1/WAF1) demonstrated G1 cell-cycle arrest and subsequently differentiated into monocytes. The latter event was associated with a cytoplasmic expression of nuclear p21(Cip1/WAF1), concomitantly with a resistance to various apoptogenic stimuli. Biochemical analysis showed that cytoplasmic p21(Cip1/WAF1) forms a complex with the **apoptosis signal-regulating kinase 1** (ASK1) and inhibits stress-activated MAP **kinase** cascade. Expression of a deletion mutant of p21(Cip1/WAF1) lacking the nuclear localization signal (DeltaNLS-p21) did not induce cell cycle arrest nor monocytic differentiation, but led to an **apoptosis**-resistant phenotype, mediated by binding to and inhibition of the stress-activated ASK1 activity. Thus, cytoplasmic p21(Cip1/WAF1) itself acted as an inhibitor of **apoptosis**. Our findings highlight the different functional roles of p21(Cip1/WAF1), which are determined by its intracellular distribution and are dependent on the stage of differentiation.

L33 ANSWER 11 OF 15 MEDLINE

ACCESSION NUMBER: 2000029738 MEDLINE

DOCUMENT NUMBER: 20029738 PubMed ID: 10561491

TITLE: Hematopoietic lineage cell specific protein 1 associates with and down-regulates protein **kinase** CK2.

AUTHOR: Ruzzene M; Brunati A M; Sarno S; Donella-Deana A; Pinna L A  
CORPORATE SOURCE: Dipartimento di Chimica Biologica and Centro per lo Studio delle Biomembrane del CNR, University of Padova, Viale G. Colombo, 335121, Padova, Italy.

SOURCE: FEBS LETTERS, (1999 Nov 12) 461 (1-2) 32-6.  
Journal code: 0155157. ISSN: 0014-5793.

PUB. COUNTRY: Netherlands  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912

ENTRY DATE: Entered STN: 20000113  
Last Updated on STN: 20020420  
Entered Medline: 19991214

AB The catalytic (alpha) subunit of protein **kinase** CK2 and the hematopoietic specific protein 1 (HS1) display opposite effects on Ha-ras induced fibroblast transformation, by enhancing and counteracting it, respectively. Here we show the occurrence of physical association between HS1 and CK2alpha as judged from both far Western blot and plasmon resonance (BIAcore) analysis. Association of HS1 with CK2alpha is drastically reduced by the deletion of the HS1 C-terminal region (403-486) containing an SH3 **domain**. HS1, but not its deletion mutant HS1 Delta324-393, lacking a sequence similar to an acidic stretch of the **regulatory** beta-subunit of CK2, inhibits **calmodulin** phosphorylation by CK2alpha. These data indicate that HS1 physically interacts with CK2alpha and down-regulates its activity by a mechanism similar to the beta-subunit.

L33 ANSWER 12 OF 15 MEDLINE

ACCESSION NUMBER: 1999003259 MEDLINE  
DOCUMENT NUMBER: 99003259 PubMed ID: 9786912  
TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein kinase that trigger **apoptosis**.  
AUTHOR: Sanjo H; Kawai T; Akira S  
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421  
ENTRY MONTH: 199812  
ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 20020420  
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic domains are related to that of death-associated protein kinase, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic domain and the C-terminal domain that is responsible for regulation of kinase activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro kinase assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the kinase activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L33 ANSWER 13 OF 15 MEDLINE  
ACCESSION NUMBER: 1998211933 MEDLINE  
DOCUMENT NUMBER: 98211933 PubMed ID: 9545236  
TITLE: Caspase-mediated activation and induction of **apoptosis** by the mammalian Ste20-like kinase Mst1.  
AUTHOR: Graves J D; Gotoh Y; Draves K E; Ambrose D; Han D K; Wright M; Chernoff J; Clark E A; Krebs E G  
CORPORATE SOURCE: Department of Immunology, University of Washington Medical Center, Seattle, WA 98109, USA.  
CONTRACT NUMBER: GM37905 (NIGMS)  
GM42508 (NIGMS)  
SOURCE: EMBO JOURNAL, (1998 Apr 15) 17 (8) 2224-34.  
Journal code: 8208664. ISSN: 0261-4189.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199806  
ENTRY DATE: Entered STN: 19980708  
Last Updated on STN: 20020420  
Entered Medline: 19980624

AB Mst1 is a ubiquitously expressed **serine-threonine kinase**, homologous to the budding yeast Ste20, whose physiological regulation and cellular function are unknown. In this paper we

show that Mst1 is specifically cleaved by a caspase 3-like activity during **apoptosis** induced by either cross-linking CD95/Fas or by staurosporine treatment. CD95/Fas-induced cleavage of Mst1 was blocked by the cysteine protease inhibitor ZVAD-fmk, the more selective caspase inhibitor DEVD-CHO and by the viral serpin CrmA. Caspase-mediated cleavage of Mst1 removes the **C-terminal regulatory domain** and correlates with an increase in Mst1 activity in vivo, consistent with caspase-mediated cleavage activating Mst1. Overexpression of either wild-type Mst1 or a truncated mutant induces morphological changes characteristic of **apoptosis**. Furthermore, exogenously expressed Mst1 is cleaved, indicating that Mst1 can activate caspases that result in its cleavage. **Kinase**-dead Mst1 did not induce morphological alterations and was not cleaved upon overexpression, indicating that Mst1 must be catalytically active in order to mediate these effects. Mst1 activates MKK6, p38 MAPK, MKK7 and SAPK in co-transfection assays, suggesting that Mst1 may activate these pathways. Our findings suggest the existence of a positive feedback loop involving Mst1, and possibly the SAPK and p38 MAPK pathways, which serves to amplify the apoptotic response.

L33 ANSWER 14 OF 15 MEDLINE

ACCESSION NUMBER: 1998416694 MEDLINE

DOCUMENT NUMBER: 98416694 PubMed ID: 9739089

TITLE: Crystal structure of JNK3: a **kinase** implicated in neuronal **apoptosis**.

AUTHOR: Xie X; Gu Y; Fox T; Coll J T; Fleming M A; Markland W; Caron P R; Wilson K P; Su M S

CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, MA 02139-4211, USA.

SOURCE: STRUCTURE, (1998 Aug 15) 6 (8) 983-91. Journal code: B31; 9418985. ISSN: 0969-2126.

PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: PDB-1JNK

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115  
Last Updated on STN: 20000303  
Entered Medline: 19981208

AB BACKGROUND: The c-Jun N-terminal **kinases** (JNKs) are members of the mitogen-activated protein (MAP) **kinase** family, and **regulate** signal transduction in response to environmental stress. Activation and nuclear localization of JNK3, a neuronal-specific isoform of JNK, has been associated with hypoxic and ischemic damage of CA1 neurons in the hippocampus. Knockout mice lacking JNK3 showed reduced **apoptosis** of hippocampal neurons and reduced seizure induced by kainic acid, a glutamate-receptor agonist. Thus, JNK3 may be important in the pathology of neurological disorders and is of significant medical interest. RESULTS: We report here the structure of unphosphorylated JNK3 in complex with adenylyl imidodiphosphate, an ATP analog. JNK3 has a typical **kinase** fold, with the ATP-binding site situated within a cleft between the N- and **C-terminal domains**. In contrast to other known MAP **kinase** structures, the ATP-binding site of JNK3 is well ordered; the glycine-rich nucleotide-binding sequence forms a beta-strand-turn-beta-strand structure over the nucleotide. Unphosphorylated JNK3 assumes an open conformation, in which the N- and **C-terminal domains** are twisted apart relative to their positions in cAMP-dependent protein **kinase**. The rotation leads to the misalignment of some of the catalytic residues. The phosphorylation lip of JNK3 partially blocks the substrate-binding site. CONCLUSIONS: This is the first JNK structure to be



determined, providing a unique opportunity to compare structures from the three MAP **kinase** subfamilies. The structure reveals atomic-level details of the shape of JNK3 and the interactions between the **kinase** and the nucleotide. The misalignment of catalytic residues and occlusion of the active site by the phosphorylation lip may account for the low activity of unphosphorylated JNK3. The structure provides a framework for understanding the substrate specificity of different JNK isoforms, and should aid the design of selective JNK3 inhibitors.

L33 ANSWER 15 OF 15 MEDLINE  
 ACCESSION NUMBER: 97474480 MEDLINE  
 DOCUMENT NUMBER: 97474480 PubMed ID: 9335504  
 TITLE: Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1.  
 AUTHOR: Kretzschmar M; Doody J; Massague J  
 CORPORATE SOURCE: Cell Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.  
 SOURCE: NATURE, (1997 Oct 9) 389 (6651) 618-22.  
 Journal code: NSC; 0410462. ISSN: 0028-0836.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199711  
 ENTRY DATE: Entered STN: 19971224  
 Last Updated on STN: 20000303  
 Entered Medline: 19971103

AB The growth factor TGF-beta, bone morphogenetic proteins (BMPs) and related factors **regulate** cell proliferation, differentiation and **apoptosis**, controlling the development and maintenance of most tissues. Their signals are transmitted through the phosphorylation of the tumour-suppressor SMAD proteins by receptor protein **serine/threonine kinases** (RS/TKs), leading to the nuclear accumulation and transcriptional activity of SMAD proteins. Here we report that Smad1, which mediates BMP signals, is also a target of mitogenic growth-factor signalling through epidermal growth factor and hepatocyte growth factor receptor protein tyrosine **kinases** (RTKs). Phosphorylation occurs at specific **serines** within the region linking the inhibitory and effector **domains** of Smad1, and is catalysed by the Erk family of mitogen-activated protein **kinases**. In contrast to the BMP-stimulated phosphorylation of Smad1, which affects **carboxy-terminal serines** and induces nuclear accumulation of Smad1, Erk-mediated phosphorylation specifically inhibits the nuclear accumulation of Smad1. Thus, Smad1 receives opposing **regulatory** inputs through RTKs and RS/TKs, and it is this balance that determines the level of Smad1 activity in the nucleus, and so possibly the role of Smad1 in the control of cell fate.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULIN  
 L2 110146 S CALMODULIN  
 L3 342878 S SERINE OR THREONINE  
 L4 73725 S L3 AND KINASE  
 L5 6021 S L2 AND L4  
 L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
 L7 391 S L5 AND L6

L8 195 S HUMAN AND L7  
 L9 1023024 S DOMAIN?  
 L10 111 S L7 AND L9  
 L11 345 S DAP(A) KINASE?  
 L12 72 S L10 AND L11  
 L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
 L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W) END OR C-TERMINAL  
 L15 34 S L10 AND L14  
 L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
 L17 10019 S "DAP"  
 L18 6 S L16 AND L17  
 L19 4269 S "ZIP"  
 L20 2 S L16 AND L19  
 L21 98 S "DRP-1"  
 L22 1 S L16 AND L21  
 E KIMCHI A/AU  
 L23 484 S E3  
 L24 3 S L16 AND L23  
 L25 3 DUP REM L24 (0 DUPLICATES REMOVED)  
 L26 1 S L25 AND DRP##  
 L27 7 S L23 AND DRP##  
 L28 2 DUP REM L27 (5 DUPLICATES REMOVED)  
 L29 81 S L23 AND L17  
 L30 18 S L29 AND L14  
 L31 6 DUP REM L30 (12 DUPLICATES REMOVED)  
 L32 15 S L16 AND REGULAT?  
 L33 15 DUP REM L32 (0 DUPLICATES REMOVED)

=> s "death domain?"

L34 3919 "DEATH DOMAIN?"

=> s l15 and l34

L35 19 L15 AND L34

=> dup rem l35

PROCESSING COMPLETED FOR L35

L36 5 DUP REM L35 (14 DUPLICATES REMOVED)

=> d 1-5 ibib ab

L36 ANSWER 1 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2002:89428 SCISEARCH

THE GENUINE ARTICLE: 513UP

TITLE: DAP **kinase** activity is critical for  
C-2-ceramide-induced **apoptosis** in PC12 cells

AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S;  
Uchino S

CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,  
Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,  
Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi  
Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut  
Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan

COUNTRY OF AUTHOR: Japan

SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.  
1, pp. 139-147.

Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD,  
OXFORD OX2 ONE, OXON, ENGLAND.

ISSN: 0014-2956.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 41

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. DAP **kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30  $\mu$ M C-2-ceramide, both the total (assayed in the presence of  $\text{Ca}^{2+}$ /calmodulin) and  $\text{Ca}^{2+}$ /calmodulin-independent (assayed in the presence of EGTA) DAP **kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30  $\mu$ M C-2-ceramide, the  $\text{Ca}^{2+}$ /calmodulin independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated DAP **kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase DAP **kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type DAP **kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive DAP **kinase** mutant and a construct containing the **death domain** and **C-terminal** tail of DAP **kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that DAP **kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic DAP **kinase** activity is critical for ceramide-induced **apoptosis**.

L36 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:43345 HCAPLUS

DOCUMENT NUMBER: 136:319709

TITLE: Transcriptional profiling reveals global defects in energy metabolism, lipoprotein, and bile acid synthesis and transport with reversal by leptin treatment in Ob/ob mouse liver

AUTHOR(S): Liang, Chien-Ping; Tall, Alan R.

CORPORATE SOURCE: Division of Molecular Medicine, Department of Medicine, Columbia University, New York, NY, 10032, USA

SOURCE: Journal of Biological Chemistry (2001), 276(52), 49066-49076

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Leptin, a hormone secreted by adipose tissue, has been shown to have a major influence on hepatic lipid and lipoprotein metab. To characterize changes in lipid and lipoprotein gene expression in mouse liver, suppression subtractive hybridization and cDNA microarray anal. were used to identify mRNAs differentially expressed after leptin treatment of ob/ob mice. Ob/ob mice showed a profound decrease in mRNAs encoding genes controlling bile acid synthesis and transport as well as a variety of apolipoprotein genes and hepatic lipase with reversal upon leptin administration, suggesting that leptin coordinately regulates high d. lipoprotein and bile salt metab. Leptin administration also resulted in decreased expression of genes involved in fatty acid and cholesterol synthesis, glycolysis, gluconeogenesis, and urea synthesis, and increased expression of genes mediating fatty acid oxidn., ATP synthesis, and oxidant defenses. The changes in mRNA expression are consistent with a switch in energy metab. from glucose utilization and fatty acid synthesis

to fatty acid oxidn. and increased respiration. The latter changes may produce oxidant stress, explaining the unexpected finding that leptin induces a battery of genes involved in antioxidant defenses. Expression cluster anal. revealed responses of several sets of genes that were kinetically linked. Thus, the mRNA levels of genes involved in fatty acid and cholesterol synthesis are rapidly (<1 h) repressed by leptin administration, in assocn. with an acute decrease in plasma insulin levels and decreased sterol regulator element-binding protein-1 expression. In contrast, genes participating in fatty acid oxidn. and ketogenesis were induced more slowly (24 h), following an increase in expression of their common regulatory factor, peroxisome proliferator-activated receptor .alpha.. However, the regulation of genes involved in high d. lipoprotein and bile salt metab. shows complex kinetics and is likely to be mediated by novel transcription factors.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 5 MEDLINE . DUPLICATE 1  
 ACCESSION NUMBER: 2001434353 MEDLINE  
 DOCUMENT NUMBER: 21214809 PubMed ID: 11313698  
 TITLE: DAP-kinase: from functional gene cloning to establishment of its role in apoptosis and cancer.  
 AUTHOR: Cohen O; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.  
 Ref: 39  
 Journal code: C7U; 9437445. ISSN: 1350-9047.  
 PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200108  
 ENTRY DATE: Entered STN: 20010806  
 Last Updated on STN: 20010806  
 Entered Medline: 20010802

AB DAP-kinase is a pro-apoptotic Ca(2+) calmodulin-regulated serine/threonine kinase that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein kinase is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death domain. The death promoting effects of DAP-kinase depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death domain. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory domain whose effect is relieved by binding to Ca(2+)-activated calmodulin. A second mode of autoinhibition engages the serine-rich C-terminal tail, spanning the last 17 amino acids of the protein. A link between DAP-kinase and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-kinase's 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-kinase was also

studied experimentally in mouse model systems where the re-introduction of **DAP-kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP-kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with **DAP-kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L36 ANSWER 4 OF 5 MEDLINE DUPLICATE 2  
 ACCESSION NUMBER: 2000144081 MEDLINE  
 DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
 TITLE: A functional genetic screen identifies regions at the **C-terminal tail and death-domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.  
 AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200003  
 ENTRY DATE: Entered STN: 20000330  
 Last Updated on STN: 20000330  
 Entered Medline: 20000323

AB Death-associated protein **kinase** (**DAP-kinase**) is a  $\text{Ca}^{+2}$ /**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP-kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP-kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP-kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the **death domain**, and the **C-terminal** tail of **DAP-kinase**. Molecular modeling of the complete **death domain** provided a structural basis for the function of the **death-domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP-kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP-kinase** apoptotic function that does not affect the catalytic activity.

L36 ANSWER 5 OF 5 MEDLINE MEDLINE DUPLICATE 3  
 ACCESSION NUMBER: 2000094983 MEDLINE  
 DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
 TITLE: Death-associated protein **kinase**-related protein  
 1, a novel **serine/threonine**  
**kinase** involved in **apoptosis**.  
 AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of  
 Science, Rehovot 76100, Israel.  
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.  
 Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420  
 Entered Medline: 20000214

AB In this study we describe the identification and structure-function  
 analysis of a novel death-associated protein (DAP) **kinase**  
 -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin**  
 (CaM)-regulated **serine threonine kinase**  
 which shows high degree of homology to DAP **kinase**. The region of  
 homology spans the catalytic **domain** and the CaM-regulatory  
 region, whereas the remaining **C-terminal** part of the  
 protein differs completely from DAP **kinase** and displays no  
 homology to any known protein. The catalytic **domain** is also  
 homologous to the recently identified ZIP **kinase** and to a lesser  
 extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP  
**kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a  
 novel subfamily of **serine/threonine kinases**.  
 DRP-1 is localized to the cytoplasm, as shown by immunostaining and  
 cellular fractionation assays. It binds to CaM, undergoes  
 autophosphorylation, and phosphorylates an exogenous substrate, the myosin  
 light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein,  
 deleted of the CaM-regulatory **domain**, was converted into a  
 constitutively active **kinase**. Ectopically expressed DRP-1  
 induced **apoptosis** in various types of cells. Cell killing by  
 DRP-1 was dependent on two features: the status of the catalytic activity,  
 and the presence of the **C-terminal** 40 amino acids  
 shown to be required for self-dimerization of the **kinase**.  
 Interestingly, further deletion of the CaM-regulatory region could  
 override the indispensable role of the **C-terminal** tail  
 in **apoptosis** and generated a "superkiller" mutant. A dominant  
 negative fragment of DAP **kinase** encompassing the **death**  
**domain** was found to block **apoptosis** induced by DRP-1.  
 Conversely, a catalytically inactive mutant of DRP-1, which functioned in  
 a dominant negative manner, was significantly less effective in blocking  
**cell death** induced by DAP **kinase**. Possible  
 functional connections between DAP **kinase** and DRP-1 are  
 discussed.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,  
 LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULAIN

L2 110146 S CALMODULIN  
 L3 342878 S SERINE OR THREONINE  
 L4 73725 S L3 AND KINASE  
 L5 6021 S L2 AND L4  
 L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
 L7 391 S L5 AND L6  
 L8 195 S HUMAN AND L7  
 L9 1023024 S DOMAIN?  
 L10 111 S L7 AND L9  
 L11 345 S DAP(A) KINASE?  
 L12 72 S L10 AND L11  
 L13 23 DUP REM L12 (49 DUPLICATES REMOVED)  
 L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W) END OR C-TERMINAL  
 L15 34 S L10 AND L14  
 L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
 L17 10019 S "DAP"  
 L18 6 S L16 AND L17  
 L19 4269 S "ZIP"  
 L20 2 S L16 AND L19  
 L21 98 S "DRP-1"  
 L22 1 S L16 AND L21  
 E KIMCHI A/AU  
 L23 484 S E3  
 L24 3 S L16 AND L23  
 L25 3 DUP REM L24 (0 DUPLICATES REMOVED)  
 L26 1 S L25 AND DRP##  
 L27 7 S L23 AND DRP##  
 L28 2 DUP REM L27 (5 DUPLICATES REMOVED)  
 L29 81 S L23 AND L17  
 L30 18 S L29 AND L14  
 L31 6 DUP REM L30 (12 DUPLICATES REMOVED)  
 L32 15 S L16 AND REGULAT?  
 L33 15 DUP REM L32 (0 DUPLICATES REMOVED)  
 L34 3919 S "DEATH DOMAIN?"  
 L35 19 S L15 AND L34  
 L36 5 DUP REM L35 (14 DUPLICATES REMOVED)

=> s "dominant negative"  
 L37 43518 "DOMINANT NEGATIVE"

=> s l16 and l37  
 L38 5 L16 AND L37

=> d 1-5 ibib ab

L38 ANSWER 1 OF 5 MEDLINE  
 ACCESSION NUMBER: 2000187596 MEDLINE  
 DOCUMENT NUMBER: 20187596 PubMed ID: 10722720  
 TITLE: Activation of MST/Krs and c-Jun N-terminal **kinases**  
 by different signaling pathways during cytotrienin  
 A-induced **apoptosis**.  
 AUTHOR: Watabe M; Kakeya H; Onose R; Osada H  
 CORPORATE SOURCE: Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi,  
 Saitama 351-0198, Japan.  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12)  
 8766-71.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200004

ENTRY DATE: Entered STN: 20000505  
Last Updated on STN: 20020420  
Entered Medline: 20000427

AB We found that antitumor drugs such as cytotrienin A, camptothecin, taxol, and 5-fluorouracil induced the activation of a 36-kDa protein **kinase** (p36 myelin basic protein (MBP) **kinase**) during **apoptosis** in human promyelocytic leukemia HL-60 cells. This p36 MBP **kinase**, which phosphorylates MBP in an in-gel **kinase** assay, results from the caspase-3-mediated proteolytic cleavage of MST/Krs protein, a mammalian Ste20-like **serine/threonine kinase**. Herein the correlation between cytotrienin A-induced **apoptosis** and the activation of MST/Krs proteins was examined in human tumor cell lines, including leukemia-, lung-, epidermoid-, cervix-, stomach-, and brain-derived cell lines. In cytotrienin A-sensitive cell lines, we observed a strong activation of p36 MBP **kinase** by cleavage of the **C-terminal** regulatory domain of full-length MST/Krs proteins by caspase-3. When the **kinase** -inactive mutant form of MST/Krs protein was overexpressed in cytotrienin A-sensitive HL-60 cells, the cytotrienin A-induced **apoptosis** was partially inhibited. Because cytotrienin A also activated c-Jun N-terminal **kinase**, we examined the effect of the expression of **dominant negative** c-Jun on cytotrienin A-induced **apoptosis**. The expression of **dominant negative** c-Jun also partially inhibited cytotrienin A-induced **apoptosis**. Furthermore, coexpression of **kinase**-inactive MST/Krs protein and **dominant negative** c-Jun completely suppressed cytotrienin A-induced **apoptosis**. These findings suggest that the proteolytic activation of MST/Krs and c-Jun N-terminal **kinase** activation are involved in cytotrienin A-induced **apoptosis** in human tumor cell lines.

L38 ANSWER 2 OF 5 MEDLINE  
ACCESSION NUMBER: 2000144081 MEDLINE  
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501  
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-domain of death-associated protein **kinase** that are critical for its proapoptotic activity.  
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A  
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
LANGUAGE: English  
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ENTRY MONTH: 200003  
ENTRY DATE: Entered STN: 20000330  
Last Updated on STN: 20000330  
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a  $\text{Ca}^{+2}$ /calmodulin-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a **dominant-negative** manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce



**apoptosis.** Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis.** We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase.** Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L38 ANSWER 3 OF 5 MEDLINE  
 ACCESSION NUMBER: 2000094983 MEDLINE  
 DOCUMENT NUMBER: 20094983 PubMed ID: 10629061  
 TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis.**  
 AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000229  
 Last Updated on STN: 20020420  
 Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase.** The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases.** DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase.** Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids

shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A **dominant negative** fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a **dominant negative** manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L38 ANSWER 4 OF 5 MEDLINE  
 ACCESSION NUMBER: 1999430101 MEDLINE  
 DOCUMENT NUMBER: 99430101 PubMed ID: 10498871  
 TITLE: Requirement of protein **kinase** (Krs/MST) activation for MT-21-induced **apoptosis**.  
 AUTHOR: Watabe M; Kakeya H; Osada H  
 CORPORATE SOURCE: Laboratory of Antibiotics, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.  
 SOURCE: ONCOGENE, (1999 Sep 16) 18 (37) 5211-20.  
 Journal code: 8711562. ISSN: 0950-9232.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199910  
 ENTRY DATE: Entered STN: 19991101  
 Last Updated on STN: 20020420  
 Entered Medline: 19991021

AB Fas is a well characterized **apoptosis**-inducing factor. One of our synthetic compounds, MT-21, induced **apoptosis** in human leukemia HL-60 cells similar to Fas. MT-21 activated caspase-3, an important cysteine aspartic protease for **apoptosis** induction. MT-21 also activated c-Jun-NH2-terminal **kinase** (JNK), a member of mitogen activated protein **kinase** (MAPK) superfamily that is involved in the regulation of cell growth, differentiation and **cell death**. Moreover, MT-21 treatment resulted in the activation of a 36 kDa **kinase** which uses myelin basic protein (MBP) as a substrate. However, MAPK and p38 were not activated by treatment with MT-21. The 36 kDa MBP **kinase** was shown to be a proteolytic product derived from the Krs protein with a molecular weight of 60 kDa. The Krs protein is a Ser/Thr protein **kinase** whose activity is enhanced by digestion of its **C-terminal** regulatory **domain** by caspase-3. When a **kinase**-inactive mutant form of Krs protein was overexpressed in HL-60 cells, JNK activation and **apoptosis** induction by MT-21 were suppressed. Furthermore, overexpression of **dominant negative** c-Jun also suppressed **apoptosis** induction by MT-21. These findings indicate that MT-21 induces **apoptosis** by the activation of JNK via the Krs protein, which is activated by caspase cleavage.

L38 ANSWER 5 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)  
 ACCESSION NUMBER: 2002:89428 SCISEARCH  
 THE GENUINE ARTICLE: 513UP  
 TITLE: DAP **kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells  
 AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S  
 CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,

Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi  
Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut  
Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan  
COUNTRY OF AUTHOR: Japan  
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.  
1, pp. 139-147.  
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD,  
OXFORD OX2 ONE, OXON, ENGLAND.  
ISSN: 0014-2956.  
DOCUMENT TYPE: Article; Journal  
LANGUAGE: English  
REFERENCE COUNT: 41

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent  
**apoptosis**. Here, we investigate the involvement of  
death-associated protein (DAP) **kinase**, initially identified as a  
positive mediator of the interferon-gamma-induced **apoptosis** of  
HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12  
cells. DAP **kinase** is endogenously expressed in these cells. On  
exposure of PC 12 cells to 30  $\mu$ M C-2-ceramide, both the total (assayed in  
the presence of  $\text{Ca}^{2+}$ /**calmodulin**) and  $\text{Ca}^{2+}$ /**calmodulin**  
-independent (assayed in the presence of EGTA) DAP **kinase**  
activities were transiently increased 5.0- and 12.2-fold, respectively, at  
10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min  
exposure to 30  $\mu$ M C-2-ceramide, the  $\text{Ca}^{2+}$ /**calmodulin** independent  
activity/total activity ratio increased from 0.22 to 0.60. These effects  
were dependent on the C-2-ceramide concentration. C-8-ceramide, another  
active ceramide analog, also induced **apoptosis** and activated DAP  
**kinase**, while C-2-dihydroceramide, an inactive ceramide analog,  
failed to induce **apoptosis** and increase DAP **kinase**  
activity. Furthermore, transfection studies revealed that overexpression  
of wild-type DAP **kinase** enhanced the sensitivity to C-2- and  
C-8-ceramide, while a catalytically inactive DAP **kinase** mutant  
and a construct containing the death **domain** and C-  
**terminal** tail of DAP **kinase**, which act in a  
**dominant-negative** manner, rescued cells from C-2-, and  
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DAP **kinase** is an important component of the apoptotic machinery  
involved in ceramide-induced **apoptosis**, and that the intrinsic  
DAP **kinase** activity is critical for ceramide-induced  
**apoptosis**.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,  
LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1 0 S CALMODULAIN  
L2 110146 S CALMODULIN  
L3 342878 S SERINE OR THREONINE  
L4 73725 S L3 AND KINASE  
L5 6021 S L2 AND L4  
L6 422053 S (CELL (A) DEATH) OR APOPTOSIS  
L7 391 S L5 AND L6  
L8 195 S HUMAN AND L7  
L9 1023024 S DOMAIN?  
L10 111 S L7 AND L9  
L11 345 S DAP (A) KINASE?  
L12 72 S L10 AND L11  
L13 23 DUP REM L12 (49 DUPLICATES REMOVED)

L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL  
 L15 34 S L10 AND L14  
 L16 17 DUP REM L15 (17 DUPLICATES REMOVED)  
 L17 10019 S "DAP"  
 L18 6 S L16 AND L17  
 L19 4269 S "ZIP"  
 L20 2 S L16 AND L19  
 L21 98 S "DRP-1"  
 L22 1 S L16 AND L21  
 E KIMCHI A/AU  
 L23 484 S E3  
 L24 3 S L16 AND L23  
 L25 3 DUP REM L24 (0 DUPLICATES REMOVED)  
 L26 1 S L25 AND DRP##  
 L27 7 S L23 AND DRP##  
 L28 2 DUP REM L27 (5 DUPLICATES REMOVED)  
 L29 81 S L23 AND L17  
 L30 18 S L29 AND L14  
 L31 6 DUP REM L30 (12 DUPLICATES REMOVED)  
 L32 15 S L16 AND REGULAT?  
 L33 15 DUP REM L32 (0 DUPLICATES REMOVED)  
 L34 3919 S "DEATH DOMAIN?"  
 L35 19 S L15 AND L34  
 L36 5 DUP REM L35 (14 DUPLICATES REMOVED)  
 L37 43518 S "DOMINANT NEGATIVE"  
 L38 5 S L16 AND L37

=>

	L #	Hits	Search Text
1	L1	22744	kinase\$2
2	L2	1802	calmodulin
3	L3	506	l1 same l2
4	L4	9798	(cell adj death) or apoptosis
5	L5	11	l3 same l4
6	L6	2	DAP adj kinase?
7	L7	0	"drp-1"
8	L8	18156	"carboxy terminal" or "c-terminal" or "carboxy end"
9	L9	38	l3 same l8
10	L10	1	l4 same l9
11	L11	20	kimchi.in.
12	L12	2	l3 and l11

	Document ID $\Delta$	Issue Date	Title
1	US 20010051335 A1	20011213	POLYNUCLEOTIDES AND POLYPEPTIDES DERIVED FROM CORN TASSEL
2	US 20020039734 A1 ✓	20020404	Compositions, kits, and methods for identification and modulation of T helper-1 and T helper-2 cells and diseases associated therewith
3	US 20020039764 A1 ✓	20020404	Nucleic, acids, proteins, and antibodies
4	US 20020040489 A1 ✓	20020404	Expressed sequences of arabidopsis thaliana
5	US 20020055627 A1 ✓	20020509	Nucleic acids, proteins and antibodies
6	US 5968816 A <i>app. 11/21/01</i> ✓	19991019	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
7	US 6025194 A ✓	20000215	Nucleic acid sequence of senescence associated gene
8	US 6090554 A ✓	20000718	Efficient construction of gene targeting vectors
9	US 6090629 A ✓	20000718	Efficient construction of gene targeting using phage-plasmid recombination
10	US 6160106 A <i>app. 11/21/01</i> ✓	20001212	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
11	US 6221647 B1 ✓	20010424	Efficient construction of gene targeting using phage-plasmid recombination

	U	1	Pages	Document ID Δ	Issue Date
1	<input checked="" type="checkbox"/>	<input type="checkbox"/>	24	US 5958748 A	19990928
2	<input checked="" type="checkbox"/>	<input type="checkbox"/>	24	US 6171841 B1	20010109

	Title	Current OR	Current XRef
1	DNA coding for serine/threonine kinase	435/194	435/252.1; 435/320.1; 435/325
2	DNA coding for serine/threonine kinase	435/194	435/252.33; 435/254.11; 435/320.1; 536/23.1; 536/23.2; 536/23.5



	Retrieval Classif	Inventor	S	C	P	2	3	4	5
1		Akira, Shizuo et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2		Akira, Shizuo et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Image Doc. Displayed	PT
1	US 5958748	<input type="checkbox"/>
2	US 6171841	<input type="checkbox"/>

	Document ID Δ	Issue Date
1	US 20010051335 A1	20011213

	Document ID $\Delta$	Issue Date	Title
1	US 5968816 A	19991019	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
2	US 6160106 A	20001212	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins